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## **Does arbovirus emergence in humans require adaptation to domestic mosquitoes?**

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### **Abstract**

In the last few decades, several mosquito-borne arboviruses of zoonotic origin have established large-scale epidemic transmission cycles in the human population. It is often considered that arbovirus emergence is driven by adaptive evolution, such as virus adaptation for transmission by ‘domestic’ mosquito vector species that live in close association with humans. Here, I argue that although arbovirus adaptation to domestic mosquito vectors has been observed for several emerging arboviruses, it was generally not directly responsible for their initial emergence. Secondary adaptation to domestic mosquitoes often amplified epidemic transmission, however this was more likely a consequence than a cause of arbovirus emergence. Considering that emerging arboviruses are generally ‘pre-adapted’ for transmission by domestic mosquito vectors may help to enhance preparedness towards future arbovirus emergence events.

## Introduction

The COVID-19 pandemic and the current outbreak of monkeypox virus are just the two most recent examples of emerging infectious diseases caused by zoonotic viruses introduced into the human population. Because humans are new hosts for these viruses, emergence is often associated with viral adaptation to human cell receptors and/or human-to-human transmission. This was the case for Ebola virus, which increased its infectivity for human cells, while reducing tropism for bat cells, during the 2013-2016 epidemic in West Africa [1]. The repeated emergence of more transmissible SARS-CoV-2 variants also represents evidence of its ongoing adaptation to human hosts [2]. However, viral adaptation to humans often does not appear to be necessary for the initial host jump. For instance, efforts to identify early adaptive mutations associated with higher human-to-human transmissibility of SARS-CoV-2 failed to identify obvious candidates [3]. Evolutionary analyses suggest that both efficient human-to-human transmission and human cell receptor usage were already present in ancestral bat-associated SARS-CoV-2 lineages [4]. In fact, SARS-CoV-2-like strains circulating in cave bats of northern Laos already have the potential to infect humans [5]. Likewise, hemorrhagic fever-causing arteriviruses circulating in wild non-human primates do not require major adaptations to replicate in human cells [6].

Here, I retrospectively examine the emergence of several mosquito-borne viruses in the last few decades to assess the extent to which viral adaptation to a new mosquito vector species was required for successful emergence in humans. The emergence of arthropod-borne viruses (arboviruses) is typically initiated by a spillover event that allows a virus to switch from a wildlife (enzootic) transmission cycle to a human (epidemic) transmission cycle. In the enzootic cycle (also referred to as the sylvatic cycle), the arbovirus is transmitted by wildlife-biting mosquito species, whereas in the human transmission cycle it is transmitted by human-biting mosquito species. This emergence scenario has been well described for yellow fever, dengue, chikungunya, and Zika viruses [7-9]. Worldwide, the two main vectors of these arboviruses are *Aedes aegypti* and *Aedes albopictus*, two 'domestic' mosquito species that thrive in human-dominated environments [10]. In addition, mosquitoes in the *Culex pipiens* complex have been involved in the emergence of West Nile virus in North America [11,12]. The initial arbovirus spillover event can be facilitated by 'bridge vectors' that bite both wild animals and humans [11-14].

Nearly all arboviruses are RNA viruses with a high evolutionary potential owing to their high mutation frequency and fast replication rate. However, the obligate host alternation of arboviruses is predicted to result in a fitness trade-off, whereby optimal replication in one host

involves a fitness cost in the other host [15]. Accordingly, arbovirus emergence via a change in host range should be less frequent than that of single-host RNA viruses. This fitness trade-off hypothesis has been supported by some studies [16], but not others [15]. In fact, adaptive evolution is generally considered a main driver of mosquito-borne virus emergence [15,17,18]. Virus adaptation to alternative mosquito vector species has often been put forward as a major factor underlying the emergence of arboviruses. For instance, emergence of a Venezuelan equine encephalitis virus genotype that caused an equine outbreak in Mexico in the 1990s was associated with a single amino-acid substitution in the envelope glycoprotein, which increased infectiousness to the mosquito vector *Ochlerotatus taeniorhynchus* [19]. In this opinion piece, I argue that adaptation to domestic vector species was typically not required for initial emergence of the most medically significant mosquito-borne viruses, although it often occurred secondarily during prolonged virus circulation in the human transmission cycle.

### **What is the evidence for arbovirus adaptation to domestic mosquitoes?**

**Yellow fever virus** is a mosquito-borne flavivirus causing a hemorrhagic fever with a case-fatality rate up to 50%. It was responsible for devastating disease outbreaks in port cities around the world from the 17<sup>th</sup> to the early 20<sup>th</sup> century [20]. Despite an effective vaccine developed in the 1930s, yellow fever virus still represents a significant public health threat because it has been increasingly re-emerging in the last few decades [20,21]. Yellow fever virus is maintained in a enzootic transmission cycle between non-human primates and sylvatic mosquitoes in jungles of Africa and South America [22]. The virus causes sporadic outbreaks when it is introduced into the human population, sometimes via an intermediate transmission cycle that bridges the sylvatic and human transmission cycles [22]. Sustained transmission of yellow fever virus in the human population is typically mediated by the domestic mosquito *Ae. aegypti*, whereas sylvatic transmission involves various mosquito species from the genus *Aedes* in Africa and from the genera *Haemagogus* and *Sabethes* in South America [7]. Although a formal investigation remains to be conducted, there is no indication in the current literature that emergence of yellow fever virus in humans was associated with adaptation for transmission by *Ae. aegypti* [23]. For example, two Brazilian strains of yellow fever virus, one isolated from a human and one isolated from a monkey, were experimentally transmitted at similar rates by Brazilian *Ae. aegypti*, *Haemagogus leucocelaenus* and *Sabethes albiprivus* [24]. The difficulty to rear the sylvatic vectors of yellow fever virus in the laboratory has been a major limitation to carry out such studies.

**Dengue viruses** also belong to the *Flavivirus* genus and are the most prevalent mosquito-borne viruses of humans – they cause disease in hundreds of millions of people each year

[25]. Four genetic types of dengue viruses evolved from sylvatic progenitors in the last hundreds of years and now circulate endemically in the human population throughout the tropics and sub-tropics [26,27]. Their worldwide emergence since the 18<sup>th</sup> century has been linked to the geographical expansion of their main mosquito vector, *Ae. aegypti* [28]. Initial dengue virus emergence in the human population required vector switching from arboreal mosquito species, such as *Aedes niveus* in Southeast Asia [8], to the domestic species *Ae. aegypti* and, to a lesser extent, *Ae. albopictus* [29]. Whether this original vector switching was associated with adaptive evolution has been debated but no conclusive evidence has been provided so far. One experimental study based on artificial blood meals found that three sylvatic dengue virus strains were less infectious to contemporaneous *Ae. aegypti* and *Ae. albopictus* mosquitoes than two human strains, supporting the idea that the latter were more adapted for transmission by domestic vectors [30]. However this result was not confirmed when an expanded repertoire of virus strains was included [15], and subsequent studies did not support the hypothesis that dengue virus emergence in humans from sylvatic progenitors required adaptation to domestic vectors [31,32]. Likewise, surrogate human models did not provide any evidence that ancestral sylvatic strains may have required adaptation to replicate more efficiently in humans [33]. Together, these experimental results are consistent with the lack of phylogenetic signature of host-specific adaptations between sylvatic and human strains [26]. On the other hand, dengue virus adaptation for enhanced transmission by *Ae. aegypti* is thought to have occurred continuously after the human transmission cycle was established. Indeed, a large body of literature supports the idea that vector-mediated selection plays a role in dengue virus lineage turnover and clade replacements [34-41]. Enhanced transmission of dengue virus by *Ae. albopictus* was also observed after 10 passages of experimental evolution *in vivo* [42]. This is in line with other studies showing that artificially bypassing one host increases arbovirus fitness in the other host [15].

**West Nile virus** is a flavivirus transmitted by *Culex* mosquitoes, which was responsible of one of the best studied arboviral emergence events after its 1999 introduction in New York and subsequent spread across North America. West Nile virus primarily infects avian hosts but it can cause disease in humans, who are dead-end hosts because they do not support onwards transmission. With the exception of one positively selected mutation encoding increased viremia in American crows [43], very little adaptive evolution has been observed during West Nile virus emergence in North America [44]. Evidence consistent with adaptation to human-biting mosquitoes was reported in two studies that found more rapid transmission of a newly arising West Nile virus lineage, which had displaced the ancestral lineage originally introduced in New York in 1999 [45,46]. These two studies found that the new lineage had a shorter extrinsic incubation period in *Culex pipiens* and *Culex tarsalis* mosquitoes, however this result

was not confirmed by another study in *Cx. tarsalis* [47]. Evidence for adaptive evolution was also reported in a more recent lineage that showed increased transmissibility and increased prevalence in New York state [48]. Overall, the rapid establishment and spread of West Nile virus following its introduction into the New World is more consistent with 'pre-adaptation' to North American vectors [15].

**Chikungunya virus** is an alphavirus that caused millions of cases of severe and often chronic arthralgia during human outbreaks in the last two decades. Chikungunya virus originates from Africa where it is maintained in a enzootic cycle involving several species of arboreal mosquito vectors and diverse non-human primates and possibly other vertebrate hosts [49]. The best documented chikungunya emergence events occurred in 2005-2006 on islands of the Indian Ocean and in 2014-2015 after introduction of the virus into the Americas [50]. Disease outbreaks resulted from the establishment of a human transmission cycle involving *Ae. aegypti* and sometimes *Ae. albopictus* [49]. The Indian Ocean outbreaks were associated with the rise of a single mutation in the envelope glycoprotein of the virus (E1-A226V) that enhances transmission by *Ae. albopictus*, but not by *Ae. aegypti* [51,52]. The E1-A226V substitution confers a clear selective advantage in places where *Ae. albopictus* is the predominant vector species. The emergence of this mutation was replicated under laboratory conditions [53] and has become a textbook example of arbovirus adaptation to an alternative mosquito vector species. However, the adaptive nature of the E1-A226V substitution is constrained by epistatic interactions that depend on the viral genetic background [54,55]. There is also ample evidence that chikungunya virus emergence in the human population did not require this mutation or adaptive evolution in general. Chikungunya virus was first discovered in present-day Tanzania during a human outbreak in 1952 [56,57] and subsequently detected in Asia in 1958 during a human outbreak in Thailand [58]. In fact, chikungunya virus may have emerged in Asia as early as the 18<sup>th</sup> century [59]. Although E1-A226V was selected convergently on at least four separate occasions during the Indian Ocean outbreaks, this adaptive substitution was not responsible for the initial emergence because it is absent from early outbreak isolates [60]. In addition, the chikungunya virus strain that was introduced into the Caribbean in 2013 lacked the E1-A226V mutation, and this mutation has not been detected during the subsequent epidemic spread in the Americas.

**Zika virus** is a mosquito-borne flavivirus that was first isolated from a sentinel monkey in Uganda in 1947 [61]. During 60 years after its discovery, it was only associated with less than 20 documented human cases and considered innocuous. The first recorded human epidemic of Zika virus occurred in Yap, Micronesia in 2007, where *Aedes hensilli* is thought to have been the main vector [62]. Zika virus subsequently spread to other islands of the South Pacific and

was introduced into Latin America in 2015 [63]. The massive epidemic that followed revealed the ability of Zika virus to cause congenital defects and neurological complications and led the World Health Organization to consider Zika virus a public health emergency of international concern. Zika virus is maintained in an enzootic transmission cycle between non-human primates and arboreal *Aedes* species, whereas transmission in the human cycle is primarily mediated by *Ae. aegypti* [64-66]. The role of adaptive evolution during the spread of Zika virus from the Asia-Pacific region to the Americas has been much debated [67-70]. Reverse genetics studies identified at least four genetic substitutions that preceded Zika virus spread into the South Pacific and the Americas and increased transmission by *Ae. aegypti* [71,72]. However, all four of these substitutions correspond to reversions that restored viral fitness after previous fixation of transmission-reducing mutations, possibly due to founder effects [71,73]. In other words, ancestral Zika virus strains did possess the nucleotide variants associated with high transmissibility by *Ae. aegypti* and were thus 'pre-adapted' for transmission in the human cycle. In fact, contemporaneous Zika virus strains currently circulating in the sylvatic cycle are more transmissible than epidemic strains that were isolated during the recent outbreaks [74].

## Conclusions

Retrospective examination of the best studied mosquito-borne arboviruses that have emerged or re-emerged in the last few decades (yellow fever, dengue, West Nile, chikungunya and Zika viruses) indicates that adaptation to domestic mosquito species that act as epidemic vectors likely does not represent a major barrier to initial arbovirus emergence. On several occasions, arbovirus adaptation to domestic mosquitoes contributed to amplify outbreaks but it was not responsible for the initial vector switching. The available evidence is consistent with the idea that emerging mosquito-borne arboviruses are generally 'pre-adapted' to transmission by domestic mosquito vectors. Once the epidemic transmission cycle is established, prolonged circulation in the human population provides increased opportunities for the arbovirus to acquire mutations that further optimize transmission by domestic mosquitoes (Figure 1). This is because the relative strength of natural selection and genetic drift depends on the population size [75]. In small populations, stochastic sampling of variants counteracts selection and hinders adaptation, whereas in larger populations, competition between virus variants occurs with little interference of random processes. Such secondary adaptation for human transmission during large-scale epidemic amplification was observed for Ebola virus [1] and SARS-CoV-2 [2]. Secondary adaptation after pathogen emergence is epidemiologically meaningful and its importance for public health should not be minimized. However, the lack of major constraint to cross the species barrier between enzootic and epidemic mosquito vectors means that initial arbovirus emergence and maintenance depend primarily on ecological rather

than evolutionary processes. Considering that an evolutionary mechanism is not a prerequisite to arbovirus emergence emphasizes the value of risk assessment studies based on the survey and characterization of arboviruses that are naturally circulating in enzootic transmission cycles. Thus, studies on the physiological competence of hosts and vectors, as well as their ecological interactions [76], should provide a relevant assessment of the risk of arbovirus emergence in the human population.

### **Conflict of interest statement**

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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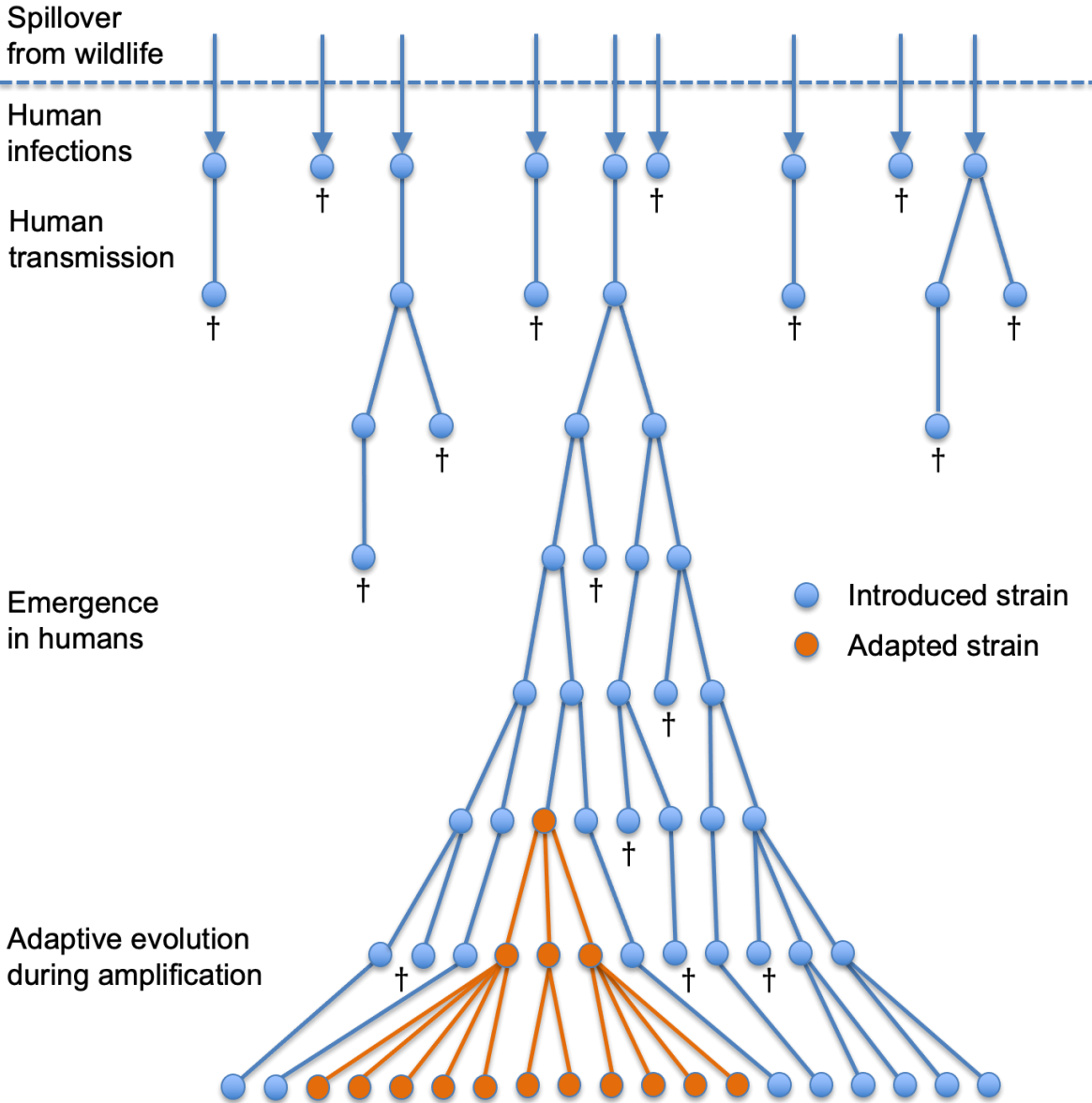
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Figure



**Figure 1. Schematic for the emergence of a zoonotic pathogen with secondary adaptation for human transmission during epidemic amplification.** Introductions from the zoonotic transmission cycle are followed by chains of transmission in the human population. Dagggers indicate no further transmission. Blue circles represent human infections with the introduced strain whereas orange circles represent infections with an evolved strain that is more adapted for human transmission. Adaptive evolution is more likely to occur during epidemic amplification of the introduced strain because of the larger population size.