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Vertical transmission of arboviruses in mosquitoes: A historical perspective

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ABSTRACT

Arthropod-borne viruses (arboviruses) are mainly transmitted horizontally among vertebrate hosts by blood-feeding invertebrate vectors, but can also be transmitted vertically in the vector from an infected female to its offspring. Vertical transmission (VT) is considered a possible mechanism for the persistence of arboviruses during periods unfavorable for horizontal transmission, but the extent and epidemiological significance of this phenomenon have remained controversial. To help resolve this question, we reviewed over a century of published literature on VT to analyze historical trends of scientific investigations on experimental and natural occurrence of VT in mosquitoes. Our synthesis highlights the influence of major events of public health significance in arbovirology on the number of VT publications. Epidemiological landmarks such as emergence events have significantly stimulated VT research. Our analysis also reveals the association between the evolution of virological assays and the probability of VT detection. Increased sensitivity and higher-throughput of modern laboratory assays resulted in enhanced VT detection. In general, VT contribution to arbovirus persistence is likely modest because vertically infected mosquitoes are rarely observed in nature. Taken together, however, our results call for caution when interpreting VT studies because their conclusions are context- and method-dependent.

1. Introduction

According to the United States Center for Disease Control and Prevention (CDC) Arbovirus Catalog (Centers for Disease Control and Prevention, 2010), there are currently at least 530 identified arthropod-borne viruses (arboviruses), of which about a hundred cause human disease. Among them, four major viral genera account for the majority of arboviral diseases: *Flavivirus* (e.g., dengue, West Nile, Japanese encephalitis, and yellow fever viruses), *Alphavirus* (e.g., chikungunya, Eastern equine encephalomyelitis, Western equine encephalomyelitis and Venezuelan equine encephalitis viruses), *Orthobunyavirus* (e.g., California encephalitis and LaCrosse viruses) and *Phlebovirus* (e.g., Rift Valley fever and sandfly fever viruses).

During the past few decades, several arboviruses have emerged globally and are now considered among the most important public health concerns for the 21st century (Gubler, 2002). Dengue, for example, has become the most prevalent arthropod-borne viral disease of humans over the last few decades (Messina et al., 2014); it has recently been estimated that there are 390 million human dengue infections each year (Bhatt et al., 2013). With only a few licensed vaccines and virtually no therapeutics available, antivectorial measures are often the only way to prevent arboviral diseases. Historically, however, the implementation of vector control measures has generally been difficult to sustain.

Arboviruses are naturally maintained in a transmission cycle between vertebrate and arthropod hosts (Gubler, 2001). The majority of arthropod hosts, generally referred to as vectors, are blood-feeding mosquitoes. Rather than a simple alternation within a single host–vector pair, arbovirus transmission often occurs through highly complex transmission networks that include various hosts and vectors (Diaz et al., 2012). Humans in particular, are not necessarily at the center of the transmission network and may only be incidental hosts (e.g., West Nile virus). Whereas some host or vector species are central to epidemic arbovirus transmission, others can be part of alternative transmission pathways, participating in the maintenance of the virus in nature during inter-epidemic periods. As an example, for some authors, fox squirrels may contribute to alternative transmission of West Nile virus in suburban communities (Root et al., 2006, 2007). In many regions of the world, climatic conditions do not allow mosquito reproduc-

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tive activity all year long. During the dry season in tropical areas or the cold season in temperate regions, the absence or low density of adult mosquitoes is unlikely to support continuous host-to-vector (horizontal) transmission (Leake, 1984). Survival of mosquitoes during dry and cold seasons involves different physiological and/or behavioral mechanisms that may impact virus transmission differently. Besides, arboviral infections in vertebrate hosts typically produce a short-lived viremic period that eventually results in immunization of the host. A high level of herd immunity in the host community may thus prevent transmission above the minimum level required for sustained horizontal transmission. The existence of reservoir host species, alternative transmission mechanism or virus re-introduction, have been proposed to explain the maintenance of arboviruses during unfavorable periods or when herd immunity is high (for review, see Reeves, 2004).

One popular hypothesis to explain the persistence of arboviruses during unfavorable periods is the occurrence of vertical transmission (VT) in the arthropod vector. In this article, we define VT as the transmission of an arbovirus from an infected female mosquito to its offspring, regardless of the underlying mechanism. VT may occur through two main mechanisms. Transovarial transmission (TOT) occurs when the virus infects the germinal tissues of the female mosquito, whereas trans-egg VT takes place during oviposition in the fully formed egg (Rosen, 1988). TOT typically achieves a higher efficiency of VT than trans-egg mechanisms especially when the germ cells are permanently infected so that most of the offspring are infected in the following generation (Tesh, 1984).

Under the VT scenario, the arbovirus present in the mosquito eggs, larvae or adults, including nulliparous females entering diapause, may survive throughout the unfavorable period without the need for a vertebrate host. Such a mixed-mode transmission (i.e., both horizontal and VT) is widespread among symbionts across taxa (Ebert, 2013). Here symbiosis is defined as any type of persistent biological interaction, which includes mutualistic, commensalistic and antagonistic relationships. Although the infection cost is often modest to the vector, arboviruses are considered parasites of mosquitoes (Lambrechts and Scott, 2009). Combining horizontal with VT enlarges considerably the range of ecological conditions in which a symbiont can persist. In host species with diapause or discrete generations, VT may allow the symbiont to endure periods when horizontal transmission is not possible. Trade-offs between the two modes of transmission have been documented but are not universal (Ebert, 2013). In addition to ecological factors that may favor horizontal over VT (e.g., climate), theory suggests that VT should be reduced in arboviruses with complex transmission networks because horizontal transmission among genetically disparate hosts hinders co-adaptation between vertically transmitted viruses and their hosts.

Both the very existence and the epidemiological significance of arbovirus VT have remained controversial since it was first suggested in the scientific literature over a century ago, at the onset of arbovirology. Carlos Finlay, who first introduced the idea of vectorial transmission of yellow fever virus by mosquitoes in 1881, extended his theory in 1899, suggesting that the yellow fever agent could be transmitted by an infected mosquito to its progeny (Finlay, 1899). During their investigations in Cuba, the Yellow Fever U.S. Army Commission proved Carlos Finlay's original theory right in 1901 and experimentally tested, albeit unsuccessfully, the possibility of yellow fever virus VT in mosquitoes (Reed et al., 1901). The same year, the Cuban physician Juan Guiteras also failed to succeed in demonstrating yellow fever virus VT (Guiteras, 1901).

Between 1901 and 1905, a group of French scientists from the Pasteur Institute carried out studies on yellow fever in Rio de Janeiro, Brazil. Among them, Paul-Louis Simond and Emile Marchoux finally demonstrated the VT hypothesis. They stated, however, that in their opinion the phenomenon was certainly infrequent (Marchoux and Simond, 1906, 1905). Following this discovery, many have tried to replicate the experiment, but none have succeeded (Davis and Shannon, 1930; Frobisher et al., 1931; Hindle, 1930; Rosenau and Goldberger, 1906).

The possibility of VT of other arboviruses was also investigated during the first half of the 20th century. Whereas early studies on dengue virus failed to provide evidence of VT (Siler et al., 1926; Simmons et al., 1931), a Japanese team demonstrated VT of Japanese encephalitis virus (Mitamura et al., 1939), but their work, published in German in a Japanese journal on the eve of World War II, went unnoticed by the scientific community. Studies on VT resumed in the 1950s and 1960s with a team from the Communicable Disease Center (ancestor of CDC) that was investigating viruses responsible for encephalitis (alphaviruses, such as Eastern equine encephalomyelitis, Western equine encephalomyelitis or Venezuelan equine encephalitis viruses; flaviviruses, such as St. Louis encephalitis virus). Their conclusions, however, were inconsistent with both positive (Chamberlain et al., 1956b; Kissling et al., 1956, 1957) and negative results (Chamberlain et al., 1956a, 1959; Chamberlain and Sudia, 1957). The outcome of these studies did not seem to depend on the virus under consideration.

In 1972, Robert B. Tesh and colleagues provided a clear demonstration of vesicular stomatitis virus VT in *Lutzomyia* sandflies (Tesh et al., 1972). The next year, another team led by Douglas M. Watts, published evidence of VT for LaCrosse virus (*Orthobunyavirus*) in experimentally infected *Aedes triseriatus* mosquitoes (Watts et al., 1973). Research on arbovirus VT by mosquito vectors has been vigorous ever since (Fig. 1), although a closer look reveals considerable heterogeneity associated with historical events and the evolution of laboratory assays used to detect VT experimentally or in a natural setting.

In the present study, we conducted a systematic review of over a century of published literature on arbovirus VT to analyze quantitatively historical trends of research on experimental and natural occurrence of VT in mosquitoes.

2. Material and methods

2.1. Literature search

Between 22 June 2011 and 25 September 2013, a systematic literature search was conducted in NCBI PubMed, ISI Web of Science, Armed Forces Pest Management Board Literature Retrieval System and Pasteur Institute Media Library. Citations in the identified articles were also examined individually in order to recover additional references. When the article was not found using the databases mentioned above, the corresponding authors and/or journal were contacted to obtain a copy of the publication. Older publications were found through Internet Archive (http://www.archive.org/).

Publications were searched regardless of their language, including English, French, German, Japanese and Chinese. Japanese and Chinese publications without a full abstract in English were excluded for practical reasons.

The review focused on arboviruses transmitted by mosquitoes and therefore articles dealing with VT in ticks or other arthropods were excluded. Likewise, publications about insect-specific viruses were excluded. Within mosquito-borne arboviruses, the review was restricted to VT in three main arboviral families: *Bunyaviridae*, *Flaviviridae* and *Togaviridae*.

2.2. Databases

Three databases were created in MySQL using the Sequel Pro© software. Contents of the three databases are described below.