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Fever versus fever: The role of host and vector susceptibility and interspecific competition in shaping the current and future distributions of the sylvatic cycles of dengue virus and yellow fever virus

Kathryn A. Hanley [a], Thomas P. Monath [b], Scott C. Weaver [c,d,e], Shannan L. Rossi [c,d,e], Rebecca L. Richman [a,f], Nikos Vasilakis [c,d,e,*]

[a] Department of Biology, New Mexico State University, Las Cruces, NM 88003, USA
[b] PaxVax, Inc., Menlo Park, CA 94025, USA
[c] Department of Pathology and Center for Biodefense and Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, TX 77555-0609, USA
[d] Center for Tropical Diseases, University of Texas Medical Branch, Galveston, TX 77555-0609, USA
[e] Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, TX 77555-0610, USA
[f] Department of Geography, New Mexico State University, Las Cruces, NM 88003, USA

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ABSTRACT

Two different species of flaviviruses, dengue virus (DENV) and yellow fever virus (YFV), that originated in sylvatic cycles maintained in non-human primates and forest-dwelling mosquitoes have emerged repeatedly into sustained human-to-human transmission by *Aedes aegypti* mosquitoes. Sylvatic cycles of both viruses remain active, and where the two viruses overlap in West Africa they utilize similar suites of monkeys and *Aedes* mosquitoes. These extensive similarities render the differences in the biogeography and epidemiology of the two viruses all the more striking. First, the sylvatic cycle of YFV originated in Africa and was introduced into the New World, probably as a result of the slave trade, but is absent in Asia; in contrast, sylvatic DENV likely originated in Asia and has spread to Africa but not to the New World. Second, while sylvatic YFV can emerge into extensive urban outbreaks in humans, these invariably die out, whereas four different types of DENV have established human transmission cycles that are ecologically and evolutionarily distinct from their sylvatic ancestors. Finally, transmission of YFV among humans has been documented only in Africa and the Americas, whereas DENV is transmitted among humans across most of the range of competent *Aedes* vectors, which in the last decade has included every continent save Antarctica. This review summarizes current understanding of sylvatic transmission cycles of YFV and DENV, considers possible explanations for their disjunct distributions, and speculates on the potential consequences of future establishment of a sylvatic cycle of DENV in the Americas.

1. Introduction: dengue and yellow fever viruses

Dengue virus (DENV) and yellow fever virus (YFV) are closely related and remarkably similar in some aspects of their natural history. Both belong to the genus *Flavivirus*, family *Flaviviridae*. All of the approximately 53 recognized species of flaviviruses (Grard et al., 2010) share a 10.6 kb, single-stranded, positive sense RNA genome comprising three structural genes and seven non-structural genes; the former make up the virion and most of the latter participate in genome replication and/or opposition of host immune defenses (Harris et al., 2006). Species in this genus cluster into one of four major clades by the taxonomy of their host as well as their mode of transmission (Cook and Holmes, 2006): (i) transmitted between vertebrate hosts by mosquitoes, (ii) transmitted among vertebrate hosts by ticks, (iii) transmitted between vertebrates without any known vector (likely by direct transmission) and (iv) directly transmitted between arthropods. Both DENV and YFV cluster with the mosquito-transmitted clade and belong to a subgroup primarily transmitted by *Aedes* mosquitoes. As discussed below, both DENV and YFV originated in sylvatic cycles, in Asia and Africa respectively, maintained in non-human primates and forest-dwelling *Aedes* mosquitoes, and both have a history of successful emergence into sustained transmission among humans by *Aedes aegypti*.

* Corresponding author. Address: Department of Pathology and Center for Biodefense and Emerging Infectious Diseases, Center for Tropical Diseases, Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, TX 77555-0609, USA. Tel.: +1 409 771 2699.
E-mail address: nivasila@utmb.edu (N. Vasilakis).

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These extensive similarities render the differences in the biogeography and epidemiology of the two viruses all the more striking. First, YFV has established a sylvatic cycle in the Americas but remains absent in Asia; whereas sylvatic DENV has spread to Africa but has not been documented in the New World (Vasilakis et al., 2011). Second, sylvatic YFV has a long history of emerging from the sylvatic cycle into urban transmission cycles among humans, but these invariably died out (Barrett and Monath, 2003). In contrast four different types of DENV have established human transmission cycles that are ecologically and evolutionarily distinct from their sylvatic ancestors (Vasilakis and Weaver, 2008). Finally, interhuman transmission of YFV has been detected only in Africa and the Americas, whereas DENV transmission among humans has been documented on every continent save Antarctica (Gubler, 2012b). Here we review the current state of knowledge about the evolution and ecology of sylvatic YFV and DENV and the factors known to influence emergence and spread of these viruses among humans. We present possible explanations for their disjunct distributions; in particular we consider whether the current distribution of sylvatic YFV and DENV reflect vagaries of trade and travel, constraints imposed by host immunity or vector competence, or indirect or direct interactions between the two viruses themselves. Finally we speculate on the likelihood and potential consequences of establishment of a sylvatic YFV cycle in Asia as well as a sylvatic DENV cycle in the Americas.

2. Transmission cycles and evolutionary dynamics of arthropod-borne viruses

Both DENV and YFV are arthropod-borne viruses (arboviruses), a group of viruses that are transmitted among vertebrate hosts by arthropod vectors and must replicate in both vertebrate and vector to perpetuate transmission (Fig. 1). This cycle of alternating infection of vertebrates and arthropods imposes substantial constraints on arbovirus evolution (Weaver, 2006). Although all arboviruses possess an RNA genome and therefore have the potential for extraordinarily rapid evolution, rates of nucleotide substitution among arthropod-transmitted viruses are often lower than those of their directly transmitted counterparts (Jenkins et al., 2002). One explanation for this paradox is the trade-off hypothesis, which proposes that mutations that enhance fitness in hosts decrease fitness in vectors and vice versa, leading to intermediate fitness phenotypes and slow rates of evolution.

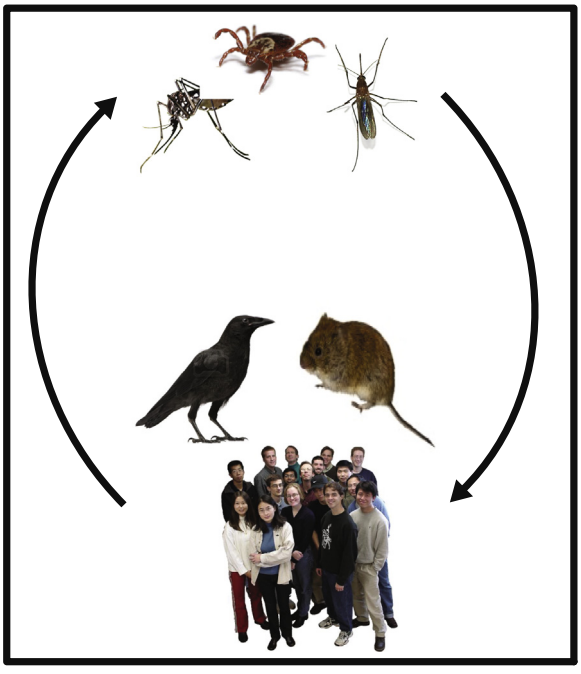

Fig. 1. The arbovirus life cycle.

If the trade-off hypothesis is correct, then release from host alternation via serial infections of a single host species should accelerate genomic evolution and lead to increased fitness the passaged host and loss of fitness in the bypassed host. To date, numerous studies have tested this prediction, using serial passage of a variety of arboviruses in vertebrate hosts and arthropod vectors in cultured cell systems and *in vivo* [reviewed in (Ciota and Kramer, 2010)]. While these studies have offered some support for the trade-off hypothesis, the results have not uniformly conformed to predictions. Moreover, phylogenetic analyses have shown that rates of evolution can differ between arboviruses that utilize different classes of vectors; for example tick-borne viruses of the genus *Flavivirus* evolve about 2.5 times more slowly than their mosquito-borne congeners (Gould et al., 2003; Zanotto et al., 1996). Indeed, even arboviruses that utilize the same hosts and vectors can show significant differences in rates of evolution; particularly salient to this review, dengue virus has an approximately 5-fold faster rate of nucleotide substitution than yellow fever virus (Sall et al., 2010). Clearly, host alternation has an impact on rates of evolution in arboviruses but host alternation alone is insufficient to explain all of the variation in these rates.

If host alternation in a single cycle is evolutionarily tricky for arboviruses, emergence into a novel transmission cycle may be doubly so. Parrish et al. (2008) have pointed out that vector transmission may enhance the potential for pathogen emergence if vectors feed broadly across host taxa. On the other hand, if vectors are highly host species-specific, then opportunities to jump into new hosts will be rare. Moreover, most such spillover events will terminate in dead-end infections of a single vector or host. Thus infection of the novel host will only occur in physical proximity to vectors that feed on the ancestral, reservoir host. Onward transmission in this cycle will require a four-way balancing act among fitness in the ancestral suite of hosts and vectors and the novel host and vector system.

Despite these obstacles, it is clear that arboviruses do regularly emerge into new transmission cycles. Notable among these are YFV, well-known for its ability to move from a jungle cycle into a devastating, albeit transient, urban cycle in humans, and DENV which has emerged from an enzootic cycle on four separate occasions to establish ecologically distinct human transmission cycles. Yet for all this apparent ecological flexibility, the ancestral, sylvatic cycles of both YFV and DENV are constrained to a subset of the geographic regions where potential hosts and vectors occur. YFV does not occur in Asia and sylvatic DENV does not occur in the New World (Fig. 2).

3. Evolutionary origins of yellow fever and dengue virus

Despite the importance of DENV for human disease, many aspects of its origin and evolution remain unclear. In particular, phylogenetic analysis of available DENV gene sequence data has only been able to resolve some aspects of DENV evolutionary history (Chen and Vasilakis, 2011). These phylogenies clearly support the hypothesis that DENV jumped from a non-human primate reservoir to humans, and that this process of cross-species transmission resulted in four sustained transmission chains in humans, creating the DENV-1 to DENV-4 serotypes that circulate in human populations today. Multiple sylvatic strains have been isolated for only two of the four serotypes, DENV-2 and DENV-4; in both of these serotypes sylvatic strains comprise genetically-distinct sister-