Complexity of virus–vector interactions

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The inter-relationships among viruses, vectors and vertebrate hosts are complex and dynamic and shaped by biotic (e.g., viral strain, vector genetics, host susceptibility) and abiotic (e.g., temperature, rainfall, human land use) factors. It is anticipated that changes in climate, as predicted by the most recent Report of the Intergovernmental Panel on Climate Change, will result in landscape changes and consequent changes in spatiotemporal patterns of arbovirus transmission. To anticipate evolving patterns of virus activity in a dynamically changing environment, it is important to understand how interconnectedness of mosquito and virus biology together with climate influence arbovirus transmission intensity. Vector competence, survivorship, and feeding behavior, among other aspects of vectorial capacity are intrinsically important to estimate risk and design control approaches.

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Introduction

Arboviruses are faced with the unique challenge of having two very disparate hosts in which they must replicate in order to perpetuate in the environment, the invertebrate vector and the vertebrate host. Together, these two hosts constitute the reservoir of the virus. The inter-relationships among viruses, vectors and vertebrate hosts are complex and dynamic and shaped by biotic (e.g., viral strain, vector genetics, host susceptibility) and abiotic (e.g., temperature, rainfall, human land use) factors. Because arthropods are ectothermic, they are highly sensitive to increases in global temperatures [1], as are the viruses they transmit. It is anticipated that changes in climate, as predicted by the recent 5th Assessment Report of the Intergovernmental Panel on Climate Change [2], will result in landscape changes and consequent

change in spatiotemporal patterns of arbovirus transmission. Understanding how arboviruses interact with mosquito vectors in such a dynamically changing environment is intrinsically important to estimate risk and design strategies to control arboviral pathogens. The intention of this review is to explore the interconnectedness of mosquito and virus biology, how that influences arbovirus transmission intensity through an impact on vector competence, survivorship, and feeding behavior; and how these aspects of mosquito biology affect vectorial capacity.

Vectorial capacity

The concept of vectorial capacity (VC), or R_0 of a pathogen, is the measure of a mosquito population's capacity to transmit an infectious agent to a new susceptible population. It integrates biotic and abiotic factors, enabling a clearer understanding of the impact of each on transmission of mosquito-borne pathogens. One basic formula for VC, a modification of [3] is $[ma^2 (I*T) p^n]/-\ln(p)$, where m is the vector density in relation to the host, a is the probability that a vector feeds on a host in one day. [A host preference index can be calculated as number of mosquitoes that blood-fed on the target host (e.g., human) minus the number that blood-fed on other vertebrates divided by the total number of mosquitoes that blood-fed on either host [4].]

The probability that a vector survives one day is p; n is the duration of the extrinsic incubation period (EIP) in days; I (infection rate) * T (transmission rate) is equal to vector competence (b) or the proportion of vectors ingesting an infective meal that are later able to transmit the infection, and $1/-\ln(p)$ is the duration of the vector's life in days after surviving the EIP. Vectorial capacity integrates viral factors with the biology of the mosquito vector. Further discussion of basic factors affecting vector competence, one aspect of VC, can be found in [5–7]. In addition, [8] among other publications, focuses on how VC of *Aedes aegypti* and *A. albopictus* impact the intensity of transmission of recent Aedes-transmitted viral threats.

Determination of VC is most informative when it takes into account subgroups of vectors that may contribute differentially to transmission risk. Therefore, refinements to the basic VC formula have been made by adding geographical, ecological, and epidemiological complexities to improve accuracy of the estimate, as VC varies spatially and temporally across a region. For example, impact of temperature on the EIP was incorporated into a dengue model [9]. A review of mathematical models of mosquito-borne pathogen transmission is presented by Reiner *et al.* [10]. In addition, there are a wide variety of

behavioral, physiological, and morphological variations among local populations of mosquitoes that could potentially impact VC [11].

Vector competence

Vector competence is one aspect of VC. It defines the ability of the mosquito to become infected with and transmit virus following an infectious blood meal [12]. Physiologic barriers to infection and dissemination [5] and the immune response following infection [13,14] have been addressed thoroughly and thus will not be covered here. The major barrier is arguably the midgut infection barrier most likely due to mosquito and virus genetics, viral dose, receptor binding, uncoating, translation, or transcription. Research is actively addressing identification of cell receptors on the midgut, which was demonstrated by Ciota and Kramer to be a major bottleneck to West Nile virus (WNV) diversity [15]. This bottleneck and others the mosquito imposes on the virus, such as infection of the salivary glands, impact viral fitness and evolution [16]. With at least one alphavirus, Venezuelan equine encephalitis (VEE) virus at high doses, midgut escape also can present a bottleneck for the virus [16]. A still unresolved question is the means by which arboviruses disseminate from the midgut. Mechanisms behind these barriers have been reviewed thoroughly [17]. Surface structures of the virus particle itself may be responsible for efficient crossing of tissue barriers [18], and/or the barrier may be physically altered during virus replication [17].

Virus and vector genetics

Vector competence is affected by both virus and vector genetics. It is well known that mosquito species differ in their ability to become infected and transmit virus, but in addition, population differences are important within single species. For example, early studies demonstrated vector competence of *Culex tarsalis* for Western equine encephalitis (WEE) and St Louis encephalitis (SLE) viruses varied spatially in California. Differences in peroral susceptibility were observed among populations collected from different locations within a contiguous geographical area as well as among cohorts of females collected as pupae from different breeding habitats sampled at the same location [19]. Similarly, vector competence of *Culex pipiens* for WNV was demonstrated [20] to vary spatially and temporally; as did Dengue virus (DENV) in different geographic populations of *A. aegypti* [21].

Viruses also demonstrate inter- and intra-serotype-specific differences in infectiousness. For example, the ID50 for DENV-1 and DENV-2 were lower than for DENV-3 and DENV-4 in one study in Vietnam [22], and the American genotype of DENV-2 was more poorly transmitted by field populations of *A. aegypti* than the Asian genotype [23•]. Even within the DENV-2 Asian–American genotype, one clade of virus had an early fitness advantage over another in *A. aegypti*, contributing to a clade replacement event [24] in Nicaragua.

Adaptive mutations in emerging virus strains may affect intensity of transmission by one species of mosquito and not another. For example, vector competence of East/Central/South African Chikungunya virus (CHIKV) by *A. albopictus* was facilitated by an amino acid change from alanine to valine at position 226 of CHIKV E1 glycoprotein (E1-A226 V), causing increased replication, midgut infection, dissemination, and transmission in this species, while no significant changes were observed in *A. aegypti*'s competence [25]. Further studies conducted on the importance of genotype × genotype × environment interactions with CHIKV examined *A. albopictus* transmission potential for CHIKV in six worldwide vector populations, with two virus strains and two ambient temperatures (20° and 28 °C) [26•]. The importance of the interaction between mosquito species, viral genetics, and temperature also was demonstrated with WNV where fixation of the E glycoprotein amino acid change A159V in WNV was facilitated by high temperatures and decreased extrinsic incubation period in *C. pipiens* and *C. tarsalis*, but not *C. quinquefasciatus* [27,28].

WNV and CHIKV adapted to the local mosquito species in naïve locations where they were introduced, as described above. Experimental studies have demonstrated that some arboviruses, for example, WNV [29], have the capacity to adapt further in that they can evolve to replicate to higher titers and more efficient transmission in their arthropod hosts. Closely related viruses, such as SLEV, appear to exist at fitness peaks and do not demonstrate the same capacity to evolve [29]. Such adaptation may be associated with costs to the vector [30] and therefore experimentally adapted virus strains might not reflect what is found in nature. Resistance to infection also was found to be costly and was observed to have an equally negative impact on mosquito biology including survivorship and egg laying patterns following infection of *C. pipiens* with mosquito-adapted WNV [31•]. This may result from cost of RNAi response in the mosquito, which plays a key role in immunity against infecting viruses [32]. Therefore, the mosquito is affected by the virus, and equally, the virus by the mosquito. Virus diversity is thought to be generated in the mosquito through relaxed purifying selection [33,34], although bottlenecks encountered as the virus replicates in the different tissues of the mosquito may restrict the presence of minority variants in the mutant swarm and thereby constrain evolution [15]. With DENV, more than 90 percent of the single nucleotide variants were lost with transmission from infected humans to *A. aegypti* and from mosquito abdomen to salivary glands, but new variants were generated at each stage of infection, thereby maintaining genetic diversity [35]. This heterogeneity of the virus population is likely important in allowing arboviruses to infect diverse hosts.