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Editorial Overview: Virus–vector interactions

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Rebecca Rico-Hesse is a Professor at Baylor College of Medicine and has worked for 30 years on tropical RNA viruses, including arthropod-borne (arboviruses) and rat-borne viruses. Her group currently works on dengue, Chikungunya, and Zika viruses, including viral evolution, replication and pathogenesis, mosquito saliva effects on immunology, and vector competence, using viral infectious clones, humanized mice, and field-collected and genetically-modified mosquitoes.

The pervasiveness of vector-borne viruses as problems of public health was made painfully clear just recently, with the emergence of Zika, a mosquito-borne virus. Although vector-borne viruses (arboviruses) were first described in the 1930s, we have yet to find consistent methods for controlling their transmission and their spread throughout most of the globe. This makes the study of the complex cycles of natural transmission of these viruses a priority for world health, as was shown by the WHO classification of the Zika epidemic as a public health emergency. Not only are these viruses important human pathogens, but many of them affect livestock and other animals, in addition to plants, thus also affecting the human population indirectly, both economically and in the limitation of food sources. Therefore, when prioritizing vector-borne virus research, not only should we think of mosquito-borne viruses, but we must include tick-borne and aphid-borne, thrip-borne, or fly-borne viruses, the first affecting mainly ungulates and causing major problems in reproduction in addition to death of animals of all ages, and the second causing rapid killing or blight of consumable plants such as wheat, tomatoes, or watermelon. In this section, an overview of the most recent developments in the understanding of the complex virus–vector cycles of disease are reviewed by an outstanding group of experts, who have summarized their opinion of what is most important.

Kramer introduces the complexity of factors that have an effect on the replication and dynamics of viruses being transmitted by invertebrates (vectors), to vertebrates (hosts), in an environment largely changing to increase the probability of transmission (climate change). She introduces the readers to the concept and equations leading to estimations of vectorial capacity, or the vectors' populational ability to transmit a virus to the susceptible host population. This is important in determining the risk of infection to the human population, and in practical terms, when and how to prioritize control methods on the vector population. These factors cannot be generalized from one vector or virus species to another, and therefore require specific measurements (lab and field) for the components of vectorial capacity to be estimated. Thus, we are only beginning to understand these estimations, and the values used as input into new models need to be measured more precisely.

Tabachnick furthers the understanding of vectorial capacity, as it is a modification of the basic reproduction number (R_0), or the number of individuals infected by a single individual, during different transmission cycles, and how complex ecological factors can determine these parameters and ultimately the number of cases of disease. The size of R_0 is determined by both biological (genetic) and environmental (abiotic) variances in an arbovirus episystem, and the goal is to reduce its value to <1, where infections and epidemics disappear. Examples are given of how temperature

and human water use can change the arbovirus episystem. However, because the specific arbovirus episystems (e.g., dengue virus in *Aedes aegypti*) vary for one location and time to another, and for one virus to another (e.g. Zika in *A. aegypti*, in the same location and time), it is important to obtain these measures for comparison, to fit the new models of epidemiologic risk, so that we may ultimately be able to predict and mitigate disease. It becomes very clear that more measurements are necessary for a unifying framework, which can incorporate the numerous heterogeneities in these virus–vector episystems.

A very good example of how temperature and other climate factors have put a new human population at risk of infection is described by Amraoui and Failloux, as they ponder the emergence of Chikungunya and its spread to Europe. Here they give very specific viral genetic and temperature changes that apparently facilitated the increased capacity of the vector (*Aedes albopictus*) to infect humans across an entirely new region of the world. The observation that a specific genotype (Eastern, Central and South African or ECSA) of Chikungunya was able to replicate, disseminate and be transmitted by French *A. albopictus* versus the same mosquitoes from other locations, even at lower temperatures (20 °C versus 28 °C), supports this conclusion. The other Chikungunya virus genotypes (West African and Asian) introduced by travellers to France or other parts of Europe did not produce autochthonous (local) transmission, nor did they grow as efficiently in the *A. albopictus*, as tested in the laboratory. This suggests a specific virus genotype — mosquito genotype pair lowers temperature adaptation for increased transmission efficiency along the Mediterranean coast, thus ensuring continued dispersal of Chikungunya and possibly other arboviruses. Lastly, these authors mention the possibility of using natural endosymbionts of *A. albopictus*, the *Wolbachia* bacteria species, to interfere with this transmission, since it is now a major concern for all of Europe.

The specifics of virus–vector evolution genetics are described in a series of papers concerning the most important emergent arboviruses affecting humans in various regions: the mosquito-borne viruses, West Nile (Grubaugh and Ebel) and dengue (Lambrechts and Lequime), and tick-borne viruses such as Tick-borne encephalitis, Powassan and Crimean-Congo (Brackney and Armstrong). The unifying themes here are: the increased potential for genetic diversity of these RNA genome viruses, due to mutation/fixation during their error-prone and rapid replication, the potential for these new variants to be selected in the hosts and vectors, at different rates, and their adaptation to novel environments, or phenotypic diversity, to develop new, natural cycles of transmission or disease presentations. These studies are the basis for determining the actual mechanisms that lead to new virus emergences, and the possibility of intervention for disease control. However, the degree of sophistication of these studies has depended on the location of the epidemics, with West Nile and Tick-borne encephalitis viruses, which emerged in developed countries (North America and Northern Europe), being the most studied. Therefore, there is a critical need for determining the evolutionary processes that lead to arbovirus emergence in the regions that have been least studied historically, before they spread to the rest of the world.

Other factors involved in arbovirus transmission that have only recently gained more interest are saliva proteins, which are injected into the host skin, as the arthropods seek to imbibe blood (which is the only reason why these vectors are interested in biting us). Wichit *et al.* describe the numerous factors (not only proteins) in mosquito saliva and how these influence the transmission and replication of dengue virus in humans. Because the contents of mosquito saliva (and other arthropod saliva for that matter) have only recently begun to be distinguished from the crude salivary gland extracts that were studied previously, it has been hard to distinguish which of these factors cause viral enhancement or inhibition. The more recent production of recombinant mosquito saliva proteins should lead to a better definition of their individual effects, and how the host immune system responds to them, thus adding to the complexity of interactions with the virus.

Other factors which have been even more difficult to measure are the effects viruses have on the numerous insects and the plants they bite or mechanically infect, and whether the arthropods biologically amplify the viruses or not in their body (propagative or not) and whether the virus is maintained inside the vector organs (circulative versus non-circulative). Although this field of research is very important economically, the numerous conditions under which viruses are transmitted by specific arthropods to different plants and how they enter their cells is only recently being defined. Here Mauck describes intriguing ways in which viruses affect their vectors to increase transmission to their plant hosts, and how these same viruses may select plant behavioral phenotypes. Plants may emit visual or odor cues to recruit vectors, can change quality or palatability cues to increase virus acquisition, and can have effects on vector movement from infected to susceptible plants, to increase virus transmission. However, there are numerous approaches (including the use of field collections of plants, characterization of viral genetic and/or epistatic effects, and the use of insect vectors for transmission studies) that have yet to be applied to understanding the basic evolutionary pressures that are applied to these arbovirus cycles, and how plant phenotypes could be selected by viruses.