A Reevaluation of the Role of *Aedes albopictus* in Dengue Transmission

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(See the major article by Whitehorn et al on pages 1182–90.)

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BACKGROUND

Vector-borne pathogen transmission cycles are complex. Understanding the factors that drive the major events of transmission—introduction, emergence, persistence, and expansion—is a sought-after goal. Dengue is a major public health concern and is spreading rapidly through tropical, subtropical, and even (transiently) temperate areas [1]. Estimates indicate that almost 100 million cases of dengue occur annually [2].

Pathogen introductions fail more often than they succeed. In 2014, for example, the Florida Department of Health Arbovirus Surveillance program reported 80 cases of dengue diagnosed in returned travelers. Despite this number, there were only 6 cases of local transmission, the timing of which suggests, at minimum, 3 small chains of transmission [3]. Additionally, there were almost 1000 cases of chikungunya virus infection diagnosed in returning travelers in the continental United States and only 11 cases of autochthonous transmission in Florida (again, likely involving several very small chains of transmission) [3]. So what confounds large-scale emergence of these pathogens? And once a pathogen has emerged, what will drive the level to which it persists? Further still, what factors will lead to expansion, either spatially, as a pathogen moves to new areas, or temporally, as the transmission season lengthens?

There are some obvious answers, including increased global travel, urbanization and habitat encroachment (for zoonoses), population susceptibility profiles, and availability of requisite vectors and climate change [1]. When assessed on a global scale, these factors may be enough to evaluate correlative relationships among variables and transmission outcomes and to predict large-scale transmission patterns, but with low precision or limited geospatial scale [4, 5].

However, understanding these transmission patterns may be more complex. Much attention has been given to the differences among and within dengue virus (DENV) serotypes with respect to vector competence. This is the intrinsic ability of a mosquito vector to support replication of a virus, leading to a disseminated infection of the salivary glands, whereby virus is expectorated upon blood feeding, culminating in a transmission event [6]. And while there are historical studies regarding DENV infection in humans [7, 8], there is less contemporary focus on the infectivity of humans to mosquitoes [9]. In this issue of *The Journal of Infectious Diseases*, Whitehorn et al present the first direct comparison of *Aedes aegypti* and *Aedes albopictus* acquisition potential by the simultaneous feeding on viremic individuals, with implications for the important transmission events listed above.

PATHOGEN INTRODUCTION

This study quantifies the transmissibility of human-associated DENV to naive mosquitoes of both species. By controlling for individual variability as they did, direct comparisons of vector infection and competence are facilitated, and valuable insights are gained. *Aedes albopictus* is not a secondary vector to *A. aegypti* by much. Acquisition rates of DENV serotype 2 (DENV-2) and DENV-4 between these two species were significantly different, while the difference between DENV-1 and DENV-3 was not significant. This is especially interesting given that DENV-1 was introduced into Florida on two separate occasions: in Key West in 2009 and in Martin County in 2013 [3, 10, 11]. *Aedes aegypti* was implicated as the primary vector of the Key West outbreak, but the details of the outbreak in Martin County remain poorly characterized [11]. Given its more temperate latitude, however, it is conceivable that the 2013 autochthonous

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transmission of DENV in Florida was due in part to *A. albopictus*.

PATHOGEN EMERGENCE

Aedes albopictus has been implicated in some small, self-limiting outbreaks [12], but the majority of transmission is facilitated through *A. aegypti*, which is thought to be a much more competent vector. Still, there has always been the possibility of DENV transmission by *A. albopictus*, namely in areas where *A. aegypti* is less abundant or absent [12]. Thus, there is a need for better characterization of transmissibility of DENV to *A. albopictus*.

The variability of human viremia in the context of vector-borne diseases not only affects disease pathogenesis and progression, but also predictions and forecasts regarding these pathogens [13]. In a previous study from the same group, it was shown that the proportion of *A. aegypti* mosquitoes with infected abdomens and, subsequently, infective saliva was dependent on the viremia level of the individual on whom the mosquitoes fed. While this was not surprising, the data represented an important quantification of this acquisition phenomenon [9]. That work was used to determine that dynamism in infectivity (related to the viremia level in an individual) can significantly affect the outcome of introduction events. In some instances, the probability of emergence of dengue was underestimated by double digits, using an average acquisition rate, rather than one tied to the viremia level of an infected person [13]. Although this was an interesting and informative pairing of field experimentation and modeling, it is only applicable to the dengue system defined by human interactions with *A. aegypti*. Thus, there is a need for better characterization of DENV in *A. albopictus,* which the current study provides. It is interesting that *A. albopictus* was significantly less efficient for dengue serotypes 2 and 4, given that DENV-1 has been implicated in outbreaks in Hawaii where *A. aegypti* was not detected and *A. albopictus* was implicated as the vector [12]. This highlights the need for further study of the potential role of *A. albopictus* in future emergence events of DENV, especially serotypes 1 and 3.

PATHOGEN PERSISTENCE

Several studies demonstrate the microevolution and within-serotype DENV diversity in transmission foci [14–16]. Specifically, genetic variability has been observed within serotypes in a well-established cohort of school children in Thailand, although the authors attribute genetic diversity to multiple introduction events [14]. In French Polynesia, investigation of genetic diversity concluded that viral evolution was ongoing during periods of endemic DENV-1 transmission and that there was evidence of more evolution during periods of endemicity than during periods of epidemic intensity [17]. One interpretation of these results is that some degree of viral genetic variability is permissible or even necessary for persistence of virus.

Whitehorn et al investigated the differences in sequence diversity of DENV-1 and concluded that there was more diversity accumulation in *A. albopictus* than in *A. aegypti,* which would seem to align with findings from the French Polynesian study [17]. However, in both cases only DENV-1 is considered (whether out of necessity or choice). Given the reported differences in dissemination of virus leading to infectious saliva among DENV serotypes and mosquito species, these data and results should be interpreted cautiously. Nevertheless, this offers some intriguing preliminary results, which will no doubt be augmented with similar studies across all 4 serotypes.

PATHOGEN EXPANSION

As climate change continues to alter the transmission landscape of arboviruses, the relative importance of *A. albopictus* will continue to increase, as it has with chikungunya virus [18]. The expansion of *A. albopictus* into large metropolises in the United States, such as Atlanta and New York City, indicate that limited seasonal transmission is possible, and autochthonous dengue was reported in Suffolk County NY in 2013 [18]. Similarly, Europe has had 19 confirmed and 2218 probable cases of autochthonous dengue between 2001 and 2012, including several in which *A. albopictus* was implicated as the probable vector. Interestingly, these outbreaks were identified as due to DENV-1 [19]. Areas where *A. albopictus* is present should be assessed for risk of DENV transmission (especially serotypes 1 and 3), given the its equal acquisition potential for all 4 DENV serotypes and the dissemination probability for DENV-1 and DENV-3. However, given the remarkable variation in viremia among individuals in both this and the previous study across all serotypes [9], there is further room to ask questions regarding strain-specific and within-serotype phenotype diversity with regard to DENV transmission potential.

CONCLUSIONS

The Whitehorn et al article presents a well-controlled experiment using humans to measure and quantify DENV transmission in a system that was as natural as possible. And while this near-natural experience has provided some intriguing and important data for the field, the article sometimes dismisses the continued value of laboratory work. Specifically mentioned are the use of an artificial feeding apparatus and laboratory mosquito strains in contrast to field-caught mosquitoes and human-provided blood meals. This is still, at its core, a carefully planned and controlled study and does not obviate the need for similarly controlled studies in laboratory settings. Further, it does not negate the importance of the findings of those studies. Despite the obvious advantages enjoyed by the use of natural vertebrate hosts, there is still a place for both mosquito-centric and nonhuman vertebrate model research in the field of DENV transmission.

The correlation by Whitehorn et al of genetic mutation accumulation and

A. albopictus abdomen titer is intriguing and warrants further study, with the potential for elucidation of midgut barrier mechanisms. Additionally, the data presented regarding viremia and viral acquisition by mosquitoes (although quite variable) may inform interesting hypotheses for in silico experiments, such as prediction of DENV emergence in interspecific competition contexts or different contact rates within and among mosquito species and human populations [13]. The results will likely lead to a rethinking of the role of *A. albopictus* in DENV transmission.

Notes

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