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Letter to the Editor

Sylvatic Dengue Viruses Share the Pathogenic Potential of Urban/Endemic Dengue Viruses

Dengue virus (DENV) exists in both sylvatic and urban/endemic ecotypes (15), and the potential for emergence of sylvatic strains has become a focus of research. Recently Mota and Rico-Hesse (10) attempted to evaluate the pathogenic potential of viruses belonging to different genetic subgroups of DENV serotype 2 (DENV-2). Based on the viremia levels and erythema index profiles of one sylvatic genotype and three (Asian, American, and Indian) urban/endemic genotypes evaluated using the NOD-*scid IL2r*γ^{null} humanized mouse model, the authors concluded that sylvatic DENV-2 viruses possess a reduced pathogenic potential compared to strains belonging to urban/endemic DENV-2 genotypes. However, these conclusions ignore both patterns in their own data and a wealth of published *ex vivo*, *in vivo*, and epidemiological evidence collected over the past 40 years.

First, Mota and Rico-Hesse (10) reported that in their mouse model, the sylvatic virus produced a peak virus titer, which is correlated with DENV disease in humans (8, 11, 18), that was significantly lower than that of the Asian genotype but higher than that of either the American or Indian genotypes. Second, the sylvatic virus caused significantly less erythema than viruses of any of the urban/endemic genotypes. However, other studies have concluded that the association of erythema with disease severity is not clear (2). Finally, thrombocytopenia, which is more directly pertinent to disease severity (1, 19), was as severe or more severe in mice infected with sylvatic DENV than in mice infected with the other DENV-2 genotypes. In sum, these data suggest that sylvatic DENV may have a potential to cause dengue disease that is equal to or greater than those of at least two established urban/endemic genotypes.

The results of Mota and Rico-Hesse (10) are consistent with previous *ex vivo* experiments utilizing monocyte-derived dendritic cells (moDCs) as a surrogate model of human infection that demonstrated no consistent differences in the level of replication of sylvatic DENV-2 strains from that of urban/endemic strains, although the Asian genotype achieved higher titers than all other genotypes (16). Similarly, *in vivo* experiments utilizing the SCID-Huh-7 xenograft mouse model yielded no consistent differences in the replication profiles between sylvatic and endemic strains (16).

The suggestion that sylvatic DENV viruses pose little risk to human health is also contradicted by several documented cases of sylvatic DENV-2 infection resulting in clinical illness indistinguishable from classic dengue fever (DF) (4, 9, 12, 14, 17). Even more compelling is a recent, severe dengue case caused by a sylvatic strain from southeast Asia, which underscores the potential of sylvatic strains to cause hemorrhagic manifestations in humans (3). All of this evidence and most of the publications cited above were ignored by Mota and Rico-Hesse (10).

Finally, Mota and Rico-Hesse (10) argue that reemergence into the urban transmission cycle by sylvatic DENV strains is unlikely for the following reasons: (i) sylvatic strains have not caused any outbreaks in West Africa, and (ii) their sylvan transmission foci are being eliminated due to human environmental disruption. While extensive environmental disruption has occurred throughout the tropics, there is strong, published evidence of continuing sylvatic DENV outbreaks as well as human and primate seroconversions in West Africa (4, 7, 17). Research sponsored by the Institut Pasteur de Dakar has documented multiple sylvatic amplification cycles occurring at roughly 8-year intervals since 1980 in West Africa (5, 6, 13, 14). The most recent amplification cycle with the isolation of sylvatic DENV-2 from mosquito collections and human infections was documented in 2008 (A. Sall, Institut Pasteur de Dakar Senegal, personal communication). The recent isolation of DENV-2 from a human patient infected in peninsular Malaysia and its close relationship to a sylvatic strain isolated nearby from a sentinel monkey in 1970 also indicate the undetected maintenance of sylvatic DENV in a zoonotic cycle in southeast Asia for nearly 4 decades (3). Thus, the assertion of Mota and Rico-Hesse (10) that sylvatic dengue virus foci have been eliminated is baseless.

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