

Dengue Human Challenge Model: Is There A Risk Caveat? Persistent Infection of Dengue Virus

Guey Chuen Perng*

Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

*Corresponding Author: Guey Chuen Perng, Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan, E-mail: gperng@mail.ncku.edu.tw

Dengue has become one of the most important vector-borne human viral diseases globally. It is estimated that about 390 million people over 100 countries are affected annually, accounting for half-million of hospitalization as well as 25,000 deaths. Majority of dengue virus (DENV) infected subjects demonstrate asymptomatic profiles, while others may develop dengue fever, and perhaps progress to severe dengue hemorrhagic fever (DHF), categorized with plasma leakage, and dengue shock syndrome (DSS). In addition, recent years, abnormal clinical manifestations apparently are rising. Despite many decades of intensive investigations, the mechanisms leading to severe dengue and/or abnormal clinical presentations remain to be further delineated. Lack of a suitable small animal model recapitulating cardinal feature of human dengue has been the major hindrance in understanding the pathogenic cause of dengue. Currently, there are no FDA approved vaccines as of today or therapeutic modalities to prevent or treat dengue. Palliative care with close monitoring is the current practice.

Cycling pattern seems to be a hallmark of dengue outbreaks in endemic regions. In many regions dengue incidence fluctuates seasonally with few if any infections reported in unfavorable periods, suggesting a strong climate effect on the vector density [1]. One of the possible hypotheses is that vertical transmission within the mosquito population [2], responsible for the outbreak patterns. The other is asymptomatic infection [3], without any noticeable illness in DENV infected humans, accounting for the spread of the disease.

Although the disease predominantly transmits during the imbibing of blood by *Aedes* mosquitoes carrying DENV, other induction routes have been documented as well. For example, the blood from healthy donors habituated in dengue endemic region appeared to be contaminated by DENV since typical dengue clinical manifestations developed in recipients upon transfusing with the healthy donated material [4,5]. Recently, screening for DENV in healthy blood donors [6] suggested that asymptomatic individuals could be potential disseminator [3]. Although infectious DENV can be isolated from this contaminated blood of healthy donors, there are very scarce of DENV specific antibodies circulating in these individuals [6]. Why does the phenomenon occur warrants further investigation. Interestingly, inapparent dengue has been coined for more than 7 decades [7], and that possible virus latency has been suggested for more than 5 decades since for a single infected individual the titer of antibody to dengue maintained at a high level after 20 years [8]. This evidence coupling with recent development on dengue, to some extent, demonstrates that persistent DENV infection may exist in the natural setting. In addition, individuals with clinical symptoms normally fully recover through time; however, the long term effects have not been

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documented or followed up. Furthermore, despite asymptomatic DENV infection accounting for large majority of the infections occurs in humans during an outbreak, their role as potential reservoir is not known.

Many questions can be raised. Do some of these people become carriers after clinical symptoms disappear? If yes, what percentage of the subjects become carriers? Can virus establish latency in some of these individuals and reactivate upon permissive conditions? What is the likely long-term effect in subject who recovers from dengue? Interestingly, in vitro studies show that dengue virus can infect persistently in a variety of tissue culture settings [9-11], and yet its significance in human counterpart has not been explored, partly due to the geographic distribution of the dengue, which makes the investigations of DENV persistent or latent infection a challenge task.

With lack of suitable animal model mimic cardinal features of severe human dengue, the human dengue challenge model is under consideration [12], the possibility of asymptomatic persistent DENV infections should be considered, examined, and the findings should be taken seriously prior to the implement the proposed human challenge model.

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