

A Putative Fifth Serotype of Dengue - Potential Implications for Diagnosis, Therapy and Vaccine Design

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Abstract

Dengue is now established as the world's most important arboviral infection. This *Aedes* mosquito-transmitted pathogen is considered to be the cause of a major re-emerging tropical disease and significant public health concern. Four distinct but genetically similar serotypes of dengue virus, DENV 1-4, are responsible for provoking a spectrum of clinical symptoms in humans that range from mild fever to severe haemorrhagic manifestations. Recently, a phylogenetically more distant fifth serotype has been mooted. Confirmation of the identification of this virus is required before its status as DENV-5 can be formally recognized. Nevertheless, the possibility of a further serotype raises the spectre of those anti-dengue therapies and vaccines predicated on DENV 1-4 that are currently under clinical trial being intrinsically suboptimal. Hence, the potential impact of the existence of DENV-5 and other sylvatic arboviruses on the strategy to combat dengue fever and related pyrexias of unknown origin should be considered in order to refine guidelines for diagnosis, treatment, prevention and control.

Today, dengue is acknowledged to be the most significant arthropod-borne viral disease of humans worldwide, with a distribution predominantly in tropical and subtropical regions that provide a natural home for its vector of transmission, female mosquitoes of the genus *Aedes* [1]. Over recent decades, the global prevalence of dengue has increased markedly, due partly to variance in genetic diversity, geographical origin and distribution of different serotypes of the virus. The disease is now endemic in excess of 100 countries in Africa, the Americas, the eastern Mediterranean, South East Asia and the Western Pacific, such that more than 2.5 billion people are at risk of infection [2]. Current global annual estimates are that approaching 400 million persons are infected by dengue, of whom a quarter present with clinical or subclinical severity [3]. Of those people, 500,000 require hospitalization for life-threatening complications, with up to 20,000 fatalities recorded as a consequence [4].

The aetiological agent of infection is the *Flavivirus* genus of family *Flaviviridae*, commonly known as Dengue Virus (DENV). This enveloped, single-stranded RNA virion is a close relative of viruses which cause other notable infectious diseases in humans such as yellow fever, Japanese encephalitis, West Nile encephalitis and hepatitis C [5]. While humans are the primary host of DENV, transmitted in particular by the peridomestic mosquito species *Aedes aegypti* and *A. albopictus*, it also infects non-human primates such as macaques [6].

In contrast to the other members of the family *Flaviviridae* mentioned above, each of which is a monotypic species, there are four well established and intimately related serotypes of dengue, DENV 1-4, that are characterized by virus plaque reduction neutralization assays [7]. The presence of multiple serotypes of DENV may be responsible for different episodes of mild to malignant disease. For example, repeated infection with heterotypic serotypes often results in severe dengue [8], as explained below, and which is a confounding factor for vaccine design.

Infection with DENV may be subclinical or symptomatic. Clinical illness is customarily classed, in order of increasing severity, as either dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). More recently, the WHO proposed a revised classification of clinical infection: dengue; dengue with warning signs;

and severe dengue [1]. DF is due to primary infection with any of the serotypes, is usually mild and self-limiting, and from which recovery is generally complete with life-long homotypic immunity. DF manifests as a fever for 2-10 days, headache, retro-orbital pain, joint and muscle pain with skin rashes [9]. Secondary infection with a heterotypic serotype generates cross-reactive antibodies the presence of which increases the potential risk of antibody-dependent enhancement of disease, a form of immunopathology. Hence, recurrent infection is the major risk factor for the serious, often fatal, complications of DHF and the rarer DSS. These are marked by problems of capillary permeability, a reduced platelet count, disordered blood clotting and severe bleeding, which, for DSS, alongside systemic shock leads to organ failure [1,8].

Different dengue serotypes vary in their capacity to cause severe illness, but there is no clear consensus on the association between the two [8]. At present, there is neither specific anti-dengue therapy nor a preventive vaccine available commercially to combat this globally resurgent public health problem [10,11]. The existence of multiple DENV serotypes in the same locality is a major threat to resident communities [1,12].

There has been considerable excitement of late within the dengue research community regarding the possibility of a fifth serotype of the virus, provisionally termed DENV-5 [13-16]. However, this editorial offers a note of caution to such speculation – official ratification of a separate serotype awaits the recovery of an isolate, which should be characterized by performing a series of rigorous identification tests to confirm, or indeed conversely to refute, its uniqueness. The putative novel serotype was discovered during screening of virus samples which were collected during an outbreak of dengue in Malaysia in 2006. The four recognized dengue serotypes are genetically similar,

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showing around 65% sequence homology [7], while the newer virus, though resembling closest DENV-4, is thought to be phylogenetically distinct [15].

An alternative proposal is that the Malaysian isolate may represent an as yet unidentified arbovirus which exists in a sylvatic cycle [17]. As such, infection of humans might occur as a chance event through transmission from an unknown species of non-human primate by an infectious mosquito [18]. In this case, the person infected may be considered as an incidental host. The identification of this pathogen could be the tip of the iceberg in that in many settings over half of all non-malaria febrile illnesses go undiagnosed and are therefore recorded as fevers, or pyrexias, of unknown origin (PUOs) [19-21]. It is likely that many of these are caused by still to be identified arboviruses [22,23]. This acknowledgment may have an impact on diagnosis and treatment as well as influencing the (re)design of candidate vaccine formulations [24,25].

For dengue, it is optimal to construct a vaccine that is simultaneously effective against all known serotypes; thus, the formulation must be tetravalent, or arguably now pentavalent [26]. All prototype vaccines under development are founded on the principle of eliciting a primary immune response that confers protection from illness by producing DENV-neutralizing antibodies [27], so vaccine candidates target a high concentration of neutralizing antibody to all DENV serotypes [28-30]. With the possibility of DENV-5, design of a pan-serotype dengue vaccine may have to go back to the drawing board.

Competing Interests

The author declares that he has no competing interests.

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