Dengue diagnosis, treatment and vaccine design: Are efforts hampered by multiple serotypes and cross-reactivity with Zika?

Andrew W. Taylor-Robinson

Taylor-Robinson AW. Dengue diagnosis, treatment and vaccine design: Are efforts hampered by multiple serotypes and cross-reactivity with Zika? J Clin Diag Treat. 2018;1(2):50-52.

ABSTRACT: Dengue is acknowledged to be the world's foremost arboviral infection of humans. This *Aedes* mosquito-borne pathogen is recognized as the aetiological agent of a preeminent re-emerging tropical disease and serious public health threat. Four discrete but genetically similar serotypes of dengue virus, DENV 1-4, trigger a range of clinical symptoms from mild fever to severe haemorrhagic complications. The existence of a phylogenetically more distant fifth serotype was recently suggested. Verification of identity is now needed before it can be officially ratified as DENV 5. Still, the prospect of another serotype calls into question the intrinsic efficacy of anti-dengue vaccines and therapies founded on DENV 1-4 that are now being developed. Accordingly, the presence of DENV 5 and other closely related sylvatic arboviruses, such as Zika, may hamper attempts to identify and treat dengue fever and related pyrexias of unknown origin. The ramifications of this should be considered when updating protocols for diagnosis, therapy, control and prevention.

Key Words: *Dengue; Zika; Virus; Serotype; Diagnosis; Treatment; Vaccine*

Dengue is firmly established as the leading *ar*thropod-*bo*rne (arbo) viral disease of humans globally, with a primarily tropical and subtropical distribution that offers a native environment for its vector of transmission, female mosquitoes of the genus *Aedes* (1). In recent times, the worldwide incidence of dengue has raised significantly, due to a combination of differences in genetic diversity, geographical origin and distribution of distinct virus serotypes (2). The disease is currently endemic in more than a hundred countries in Central and South America, the Caribbean, the Mediterranean, Africa, South East Asia and the Western Pacific region, which places over 2.5 billion people at risk of infection (2,3). Present global estimates indicate that nearly 400 million individuals are infected by dengue each year, of who a quarter suffer clinical or subclinical illness (4). Of those persons, around 500,000 are hospitalized with life-threatening complications, of which approximately 20,000 die as a direct result (5).

DENGUE VIRUS

The causative agent of infection is the enveloped, positive-sense, single-stranded RNA virus dengue (DENV), which belongs to the *Flavivirus* genus. It is closely related to viruses that cause other noteworthy infectious diseases of humans, including yellow fever, Japanese encephalitis, West Nile encephalitis and Zika (ZIKV) (6). Humans are the primary host of DENV but non-human primates like macaques may also be infected. Transmission occurs principally via an infectious bite of the peridomestic mosquito species *Aedes aegypti* and *A. albopictus* (7).

Contrary to the other named species of the family Flaviviridae, each of which is monotypic, the dengue virus has four clearly recognized but very similar serotypes, DENV 1-4, which are distinguished by virus plaque reduction neutralization assays (8). The existence of multiple DENV serotypes may account for diverse episodes of mild to malignant disease. For instance, severe dengue frequently eventuates from repeated infection with heterotypic serotypes (9), as explained below, and which may impede rational vaccine design.

DENGUE INFECTION

Infection with DENV can be asymptomatic or clinical. By convention, clinical illness is typed, ordered by increasing severity, as dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Lately, the World Health Organization recommended a revised classification of clinical infection: dengue; dengue with warning signs; and severe dengue (1). DF is caused by primary infection with any one serotype, is generally mild and self-limiting, and recovery from which is usually followed by life-long homotypic immunity. DF presents as a febrile illness for between 2 to 10 days, with headache, retro-orbital pain, muscle ache, joint pain and skin rashes (10). Secondary infection with a heterotypic serotype invokes cross-reactive antibodies the presence of which raises the threat of antibody-dependent enhancement (ADE) of disease, an immunopathological manifestation. Recurrent infection is thus the main risk factor for the grievous, often fatal, complications of DHF and the less observed DSS. These are characterized by issues relating to a diminished platelet count, capillary permeability, disordered blood clotting and severe bleeding, which for DSS, together with systemic shock, causes organ failure (1,9).

LACK OF SPECIFIC THERAPY

Diverse dengue serotypes differ in their facility to cause serious illness, but there is a lack of unanimity among researchers as to what links the two (9). Right now, in order to resist this internationally re-emerging public health concern there is neither a specific anti-dengue preventive vaccine available nor an efficacious approved therapy (11,12). The occurrence of several DENV serotypes in the same vicinity poses a significant risk to local residents (1,13).

A NEW DENGUE SEROTYPE

Among virologists, there has been appreciable speculation of late surrounding the likelihood of a fifth serotype of DENV, conditionally designated DENV 5 (14-18). However, a word of caution should be offered to moderate conjecture; official recognition of a novel serotype awaits characterization of an isolate through a succession of stringent tests to confirm, or indeed to refute, its unique identification (18). The supposed distinctive serotype was detected by screening virus samples collected during a dengue outbreak in Malaysia in 2006. The four established DENV serotypes are similar genetically, displaying approximately 65% sequence homology (8). On the other hand, the newly found virus, although resembling DENV 4 the closest, is believed to be phylogenetically more distant (16).

CROSS-REACTIVITY WITH ZIKA

To convolute matters further, ZIKV shows around 40% similarity genetically to DENV 1-4, which has led some researchers, have gone so far to claim that it can possibly be considered akin to a DENV serotype (19). The significant degree of homology presents a threat of triggering cross-reactive immunity and consequent ADE in cases of secondary infection or for persons who are immunized (20,21). Each of these factors confounds the production of a pan-serotype prophylactic vaccine or a therapeutic drug aimed at prevention or cure of DENV and ZIKV infections (22). Additionally,

School of Health, Medical and Applied Sciences, Central Queensland University, Brisbane, QLD 4700, Australia

Correspondence: Prof. Andrew W Taylor Robinson, School of Health, Medical and Applied Sciences, Central Queensland University, Brisbane, QLD 4700, Australia. Telephone +61 07 3295 1185, e-mail a.taylor-robinson@cqu.edu.au

Received: October 20, 2018, Accepted: October 26, 2018, Published: November 01, 2018

co-infection of DENV with, and lack of rapid tests for, ZIKV may complicate the issue further in some regions of the world (23).

ZOONOTIC TRANSMISSION?

It is possible to speculate that the putative DENV 5 Malaysian isolate constitutes a still to be recognized, hitherto unknown arbovirus that circulates in a sylvatic cycle (24). Infection of humans may thus happen by chance through transmission via an infectious mosquito from an unidentified species of non-human primate (25). The infected person may be thought of as an incidental host. This scenario is much the same as that for zoonotic infection of humans with simian malaria parasites (26).

PYREXIAS OF UNKNOWN ORIGIN

The identification of a previously unknown viral pathogen could be just the beginning since in numerous locations more than half of all non-malarial febrile illnesses are not diagnosed, being reported as fevers, or pyrexias of unknown origin (27-30). It is probable that a considerable proportion of these are caused by yet to be recognized or neglected arboviruses (31-33). This realization may ultimately have a beneficial influence on clinical case diagnosis and treatment regimens as well as informing reevaluation of candidate vaccine designs (34,35).

RETHINKING VACCINE DESIGN

In considering a vaccine to prevent dengue it is most advantageous to be effective concurrently against each known serotypes; therefore, the construct should be tetravalent, or perhaps now pentavalent (36). All vaccine candidates in preparation are designed on the basis of stimulating a primary immune response that elicits DENV-neutralizing antibodies to confer protection from illness (37). Thus, the goal of a prototype vaccine is to trigger elevated levels of neutralizing antibody against all DENV serotypes (38-40). With the very real prospect of DENV 5, as well as cross-reactivity with ZIKA and possibly other flaviviruses, construction of a pan-serotype dengue vaccine may require a fundamental redesign.

DECLARATION

The author declares no competing interests.

REFERENCES

1. World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: WHO. 2009;160 pp.
2. Gyawali N, Bradbury RS, Taylor-Robinson AW. The epidemiology of dengue infection: harnessing past experience and current knowledge to support implementation of future control strategies. J Vector Borne Dis. 2016;53:293-304.
3. Islam R, Salahuddin M, Ayubi MS, et al. Dengue epidemiology and pathogenesis: images of the future viewed through a mirror of the past. Virol Sin. 2015;30:326-43.
4. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496:504-07.
5. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998;11:480-86.
6. Halstead SB. Dengue. Lancet. 2007;370:1644-52.
7. Burke DS, Monath TP. Flavivirus. In: Knipe DM, Howley PM, eds. Fields Virology, vol 1, 4th ed. Philadelphia: Lippincott Williams & Wilkins. 2001:1043-1126.
8. Guzman MG, Halstead SB, Artsob H, et al. Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8:S7-S16.
9. Endy TP. Epidemiology of inapparent and symptomatic acute dengue virus infection: a prospective study of primary school children in Kamphaeng Phet, Thailand. Am J Epidemiol. 2002;156:40-51.
10. Leitmeyer KC, Vaughn DW, Watts DM, et al. Dengue virus structural differences that correlate with pathogenesis. J Virol. 1999;73:4738-47.
11. Sanyal S, Taylor-Robinson AW. Host-virus interactions in dengue infection indicate targets for detection and therapeutic interventions. Immun Dis. 2013;1:71-4.
12. Ansari S, Taylor-Robinson AW. Strategic approaches to multivalent vaccine development against dengue virus infection. Annal Vaccin Immuniz. 2014;1:1005-12.
13. Halstead SB, Heinz FX, Barrett AD, et al. Dengue virus: molecular basis of cell entry and pathogenesis. Vaccine. 2005;23:849-56.
14. Normile D. Surprising new dengue virus throws a spanner in disease control efforts. Science 2013;342:415.
15. da Silva Voorham JM. A possible fifth dengue virus serotype. Ned Tijdschr Geneeskd. 2014;158: A7946.
16. Mustafa MS, Rasotgi V, Jain S, et al. Discovery of fifth serotype of dengue virus (DENV-5): A new public health dilemma in dengue control. Med J Armed Forces India. 2015;71:67-70.
17. Wiwanitkit S, Wiwanitkit V. Acute viral hemorrhage disease: a summary on new viruses. J Acute Dis. 2015;4:277-79.
18. Taylor-Robinson AW. A putative fifth serotype of dengue – potential implications for diagnosis, therapy and vaccine design. Int J Clin Med Microbiol. 2016;1:101.
19. Singh MV, Weber EA, Singh VB, et al. Preventive and therapeutic challenges in combating Zika virus infection: are we getting any closer? J Neurovirol. 2017;23:347-57.
20. Kawiecki AB, Christofferson RC. Zika virus-induced antibody response enhances dengue virus serotype 2 replication *in vitro*. J Infect Dis. 2016;214:1357-60.
21. Paul LM, Carlin ER, Jenkins MM, et al. Dengue virus antibodies enhance Zika virus infection. Clin Transl Immunol. 2016;5:e117.
22. Taylor-Robinson AW. Cross-reactivity of non-neutralizing antibodies to dengue and Zika viruses: implications for vaccination. Arch Prev Med. 2017;2:10-14.
23. Taylor-Robinson AW. Enhancement of infection by pre-existing non-neutralizing antibodies to cross-reactive flaviviruses: ramifications for vaccination against dengue and Zika. J Vacc Clin Trials. 2017;1:1-4.
24. Vasilakis N, Durbin AP, da Rosa AP, et al. Antigenic relationships between sylvatic and endemic dengue viruses. Am J Trop Med Hyg. 2008;79:128-32.
25. Inoue S, Morita K, Matias RR, et al. Distribution of three arbovirus antibodies among monkeys (*Macaca fascicularis*) in the Philippines. J Med Primatol. 2003;32:89-94.
26. Anstey NM, Grigg MJ. Zoonotic malaria: the better you look, the more you find. J Infect Dis. 2018. https://doi.org/10.1093/infdis/jiy520.
27. Hirschmann J. Fever of unknown origin in adults. Clin Infect Dis. 1997;24:291-300.
28. Efstathiou SP, Pefanis AV, Tsiakou AG, et al. Fever of unknown origin: discrimination between infectious and non-infectious causes. Eur J Intern Med. 2010;21:137-43.
29. Susilawati TN, McBride WJH. Undiagnosed undifferentiated fever in Far North Queensland, Australia: a retrospective study. Int J Infect Dis. 2014;27:59-64.
30. Gyawali N, Bradbury RS, Aaskov JG, et al. Neglected Australian arboviruses: quam gravis? Microb Infect. 2017;19:388-401.
31. Forshey BM, Guevara C, Laguna-Torres VA, et al. Arboviral etiologies of acute febrile illnesses in Western South America, 2000-2007. PLoS Negl Trop Dis. 2010;4:e787.
32. Jentes ES, Robinson J, Johnson BW, et al. Acute arboviral infections in Guinea, West Africa, 2006. Am J Trop Med Hyg. 2010;83:388-94.
33. Gyawali N, Bradbury RS, Taylor-Robinson AW et.al. Neglected Australian arboviruses and undifferentiated febrile illness: addressing public health challenges arising from the 'Developing Northern Australia' Government policy. Front Microbiol. 2017;8:2150.
34. Subedi D, Taylor-Robinson AW. Laboratory diagnosis of dengue infection: current techniques and future strategies. Open J Clin Diagn. 2014;4:63-70.
35. Liang G, Gao X, Gould EA. Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control. Emerg Microbes Infect. 2015;4: e18.
36. Subedi D, Taylor-Robinson AW. Development of a dengue vaccine in humans: so near, yet so far. SOJ Vaccine Res. 2015;1:7-13.

37. Vannice KS, Roehrig JT, Hombach J. Next generation dengue vaccines: a review of the preclinical development pipeline. Vaccine. 2015;33:7091-99.

38. Coller BA, Clements DE. Dengue vaccines: progress and challenges. Curr Opin Immunol. 2011;23:391-98.

39. Vaughn DW, Green S, Kalayanarooj S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000;181:2-9.

40. Whitehead SS, Falgout B, Hanley KA, et al. A live, attenuated dengue virus type 1 vaccine candidate with a 30-nucleotide deletion in the 3' untranslated region is highly attenuated and immunogenic in monkeys. J Virol. 2003;77:1653-57.