

Implications of Flaviviruses cross-reactivity and vaccination programs on their serodiagnosis

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Abstract: Arboviral infections especially those caused by flaviviruses are reemerging, expanding and endemic in tropical and subtropical countries. Immunoassays are the most commonly used diagnostic laboratory method because of their low cost and less test turnaround time. However, flaviviruses share epitopes inducing cross-reactive antibodies leading to great difficulty in differentially diagnosing flaviviral infections using serological tests. Considering the availability of yellow fever, west Nile and St. Louis encephalitis virus vaccinations and recently, dengue vaccine in some countries, serodiagnosis of flaviviruses could be very complicated. This minireview was aimed at evaluating the complexity of Zika and Dengue serological differential diagnosis in resource limited settings where antigen-based and molecular assays are difficult to execute.

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1. Introduction

Taxonomically, Flaviviruses form a genus in the family *Flaviviridae* which in addition includes the genera hepacivirus and pestivirus (Thiel *et al.*, 2005). More than 70 different viruses, many of which are arthropod-borne and transmitted by either mosquitoes or ticks have so far been identified to be part of this group (Gubler *et al.*, 2007). Flaviviruses are named from the yellow fever virus, the type virus for the family; the word *flavus* means "yellow" in Latin. The name yellow fever in turn originated from its propensity to cause yellow jaundice in victims (Monath *et al.*, 2008). Human infections with these viruses are typically incidental, as humans are usually unable to replicate the virus to high enough titers to re-infect the arthropods needed to continue the virus lifecycle, human thus act as dead end host (Monath *et al.*, 2008). The exceptions to this are the yellow fever, dengue, and zika viruses, which still require mosquito vectors, but are well-enough adapted to humans as to not necessarily depend upon animal hosts (although they continue to have important animal transmission routes, as well). With regards to disease impact, flaviviruses includes the following; yellow fever virus (YFV), dengue virus (DENV), Japanese encephalitis virus (JEV), West Nile virus (WNV) and tick-borne

encephalitis virus (TBEV), and Zika virus (Gubler *et al.*, 2007). Several others can also cause severe and even lethal disease in humans but potential exposure to these viruses is apparently limited and the reported case numbers are relatively small. Examples are; St. Louis encephalitis virus, Murray valley encephalitis virus, Rocio virus, Kyasanur forest disease/Alkhurma virus, Omsk hemorrhagic fever virus and Powassan virus (Thiel *et al.*, 2005).

2. Global distribution of Flaviviruses

Due to their dependence on specific vectors and different natural hosts, flaviviruses have distinct geographical distributions. YFV is endemic in tropical and subtropical regions in Africa and South-America and causes an estimated 200,000 cases with 30,000 deaths annually (Monath *et al.*, 2008) Geographically, the endemic regions of DENV overlap with those of YFV in Africa and South-America. However, DENV extends not only to Middle America and southern parts of North America but also to large parts of South-East Asia, where YFV is not found (Vasilakis *et al.*, 2011). Infections with DENV are usually mild but extremely frequent, with about 100–200 million infections every year (Guzman *et al.*, 2010). In a small proportion of patients, the disease can aggravate and

lead to dengue hemorrhagic fever (DHF) and/or dengue shock syndrome (DSS). Studies have shown that annually about 500,000 such cases with more than 20,000 deaths are recorded (WHO, 2015). The endemic areas of JEV overlap with those of DENV in South-East Asia, but JEV is transmitted by different mosquitoes and has different natural hosts (Halstead and Thomas, 2010). JEV causes severe encephalitis and 25–30% of the 50,000 cases occurring every year are fatal (Halstead and Thomas, 2010). In contrast to these mosquito-borne viruses, TBEV is not found in the tropics/subtropics but in many parts of Europe as well as Central and Eastern Asia (Indquist and Vapalahti, 2008). In these areas, it accounts for one of the most important CNS infections in adults with more than 10,000 cases per year (WHO, 2011). WNV is an example of the potential of flaviviruses to emerge suddenly in previously unaffected geographical areas. It was known to be endemic in parts of Africa, Europe, Asia, and Australia – causing sporadic cases or small outbreaks of CNS disease – before it first appeared at the East coast of the USA in 1999 and rapidly spread over the North-American continent, to Central-America and finally to South-America (Gubler, 2007a). In the peak year of 2003, 9862 human cases and 264 deaths due to WNV infections were documented in the US (Hayes *et al.*, 2005) and because of continued expansion, the need for an effective vaccine appeared to gain high priority (Gould and Fikrig, 2004). Since then, the annual numbers of cases in the US have declined significantly, with a parallel decrease in the interest for commercial vaccine development. Zika virus is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia. From 2007 to 2016, the virus spread eastward, across the Pacific Ocean to the Americas, leading to the 2015–16 Zika virus epidemic. The Zika virus infection often causes no or only mild symptoms, similar to a very mild form of dengue fever (Malone *et al.*, 2016). As of 2016, the illness cannot be prevented by medications or vaccines. Zika can also spread from a pregnant woman to her fetus. This can result in microcephaly, severe brain malformations, and other birth defects (Rasmussen *et al.*, 2016). Zika infections in adults may result rarely in Guillain–Barré syndrome (WHO, 2016).

3. Flaviviruses vaccines: progress and prospect

The very successful yellow fever 17D vaccine, introduced in 1937, produced dramatic reductions in epidemic activity. Studies have shown that yellow fever vaccine is generally safe, this includes in those with HIV infection but without symptoms. Mild side effects may include headache, muscle pains, pain at

the injection site, fever, and rash. Severe allergies occur in about eight per million doses, serious neurological problems occur in about four per million doses, and organ failure occurs in about three per million doses. It is likely safe in pregnancy and therefore recommended among those who will be potentially exposed. (WHO, 2013) It should not be given to those with very poor immune function (CDC, 2015).

Effective inactivated Japanese encephalitis and Tick-borne encephalitis vaccines were introduced in the middle of the 20th century (CDC, 2015). Unacceptable adverse events have prompted change from a mouse-brain inactivated Japanese encephalitis vaccine to safer and more effective second generation Japanese encephalitis vaccines (Halstead and Thomas, 2010). These may come into wide use to effectively prevent this severe disease in the huge populations of Asia - North, South and Southeast. The dengue viruses produce many millions of infections annually due to transmission by a successful global mosquito vector. As mosquito control has failed, several dengue vaccines are in varying stages of development. A tetravalent chimeric vaccine that splices structural genes of the four dengue viruses onto a 17D yellow fever backbone is now available as Dengvax (WHO, 2016).

4. Flaviviruses antigenic interactions

DENV, YFV and recently Zika have led to strong epidemiological surveillance programs being developed which are focused on rapid, accurate laboratory diagnosis for the early implementation of specific preventative health measures for curtailing outbreaks and reducing disease burden (WHO, 2016). Laboratory diagnosis of infection depends on detecting specific DENV, Zika, SLEV, JEV and YFV host antibodies. Neutralization assays are considered to provide the greatest specificity from all currently available serological methods (Houghton-Triviño *et al.*, 2008). However, the enzyme immunoassay (ELISA) is the most commonly used method because of its low cost and the speed of its results; it has also been reported to be a highly specific assay (Vazquez *et al.*, 2003), although this could be difficult in flavivirus serology.

Molecular sequencing data have shown that flaviviruses exhibit significant degree of homology in their nucleotides; this feature perhaps leads to cross-reactive antibody responses to antigenic epitopes common to all flaviviruses on envelope (E) protein. These pose an important problem in serological diagnosis in areas where multiple flaviviruses circulate or where circulating neutralizing antibodies exist as result of prior vaccination (Gubler, 2007a). Such shared epitopes-induced cross-reactivity may also lead

to dramatic increase in the severity of secondary infections via antibody-dependent enhancement, particularly in the case of DENV serotypes (Gubler *et al.*, 2007b).

5. Conclusion

Despite the neutralization test being the gold standard for flavivirus serology, DENV, ZKV and YFV surveillance is based on detecting specific IgM and IgG antibodies by ELISA. The existence of cross-reactivity due to prior vaccination may thus pose a real challenge for sero-epidemiological studies and routine case confirmation of disease entities. However, it is not known whether rapid, specific differential ZKV, DENV and YFV infection diagnosis is possible in countries having limited resources or whether new experimental strategies should be designed.

6. Conflict of interest

None.

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