

The emergence and re-emergence of arboviruses: Transmission and disease burden

Nur Alia Johari

The viruses and their vectors

Arthropod-borne viruses, or arboviruses, as the name suggests, are transmitted by arthropod vectors including mosquitoes and ticks. Of particular concern are the three arboviruses viz. dengue, chikungunya and Zika that have emerged with increasing disease incidence and geographical distribution. Over the last decade we have been faced with the emergence of the Zika virus (ZIKV) in Latin America and Asia¹, along with the resurgence of the dengue (DENV) and chikungunya (CHIKV) viruses that have plagued tropical and subtropical regions from as early as the 18th century^{2,3}. The spread of these arboviruses is inherently linked to the presence of the *Aedes* vector population. The fact that all three viruses are transmitted primarily by the *Aedes aegypti* mosquito is alarming, as this means that their transmission is subject to the same extrinsic and intrinsic factors involving the vector itself, the human host and the surrounding environment. *Ae. albopictus* is also capable of transmitting these arboviruses, and along with *Ae. aegypti* are active feeders in the daytime, rendering insecticide-treated bednets that have been instrumental in the battle against malaria useless in this scenario. Furthermore, unlike *Ae. aegypti*, *Ae. albopictus* possesses a wider geographical distribution due to its characteristically stronger ecological plasticity, dominance in resource competition and resilience in a range of environmental conditions^{4,5}.

The *Aedes* vector typically thrives in warm, tropical climates that are characterised by periodic patterns of rainfall, and exhibit a preference for urban and semi-urban environments as their habitat⁶. Thus, developing countries in tropical and subtropical regions are at the greatest risk. These regions are home to a population of over 2 billion individuals, and therefore the countries affected are subject to significant health and socioeconomic burden. In 2016, the Philippines and Malaysia contributed to over 100,000 dengue cases each out of 375,000 suspected cases reported in the World Health Organization (WHO) Western Pacific (WPRO) region. In the Americas, out of over 2.38 million cases, Brazil was singlehandedly responsible

for approximately 1.5 million cases⁷. The presence of the *Aedes* mosquitoes in both rural and urban areas places these populations at risk of CHIKV and ZIKV infections as well. The epidemiology of these infections will therefore be greatly influenced by vector ecology; with cyclical patterns of outbreaks occurring based on interactions between the mosquito vector, the infecting viruses and the immunity and behaviour of susceptible human populations.

To complicate matters, dengue, chikungunya and Zika infections result in febrile illnesses with similar presenting symptoms that generally include rashes, joint and muscle pain, headache and nausea. Misdiagnosis, especially in dengue-endemic countries, is highly common. Co-infections with two or more of these diseases have also been reported, but the clinical and public health implications of such infections are still unclear, as are the mechanisms of interactions between these viruses in both the vector and the human host. As discussed by Vogels and colleagues⁸, the interactions between these viruses may determine whether co-infections within the vector and/or human host result in one of four scenarios – virus inhibition, competition, enhancement or no effect (neutral). Thus far there are limited studies on cases of clinical co-infections, with available reports indicating that disease severity in co-infected patients does not appear to be any more common than those with single infections.

The dengue virus (DENV) is a single-stranded, positive strand RNA flavivirus. The virus is in the same family as ZIKV as well as other well-known human pathogens, namely the Japanese encephalitis virus (JEV), West Nile virus (WNV) and Yellow Fever virus (YFV). DENV is divided into four different serotypes, each capable of causing infections of varying degrees of severity³. Many countries in the Western Pacific Region, including Malaysia, are dengue hyperendemic, with all four serotypes co-circulating at any one time. This poses a major challenge in its control as patients that have recovered from one DENV serotype are still susceptible to infection with another with a possibility of immune enhancement of disease⁹. Compared to DENV, CHIKV

Institute for Research, Development and Innovation, International Medical University, Bukit Jalil, 57000 Kuala Lumpur, MALAYSIA

Corresponding Author:

Nur Alia Johari, Institute for Research, Development and Innovation, International Medical University, Bukit Jalil, 57000 Kuala Lumpur, MALAYSIA
E-mail: nuraliajohari@imu.edu.my

and ZIKV are less antigenically diverse, with CHIKV patients possessing life-long immunity post-infection.

CHIKV is an alphavirus that was first isolated in the 1950s in Tanzania from both mosquitoes and human serum. The virus has since spread across Asia, resulting in outbreaks in Southeast Asia as well as India, and more recently in Italy and the Indian Ocean islands between 2005 and 2007². The greatest burden CHIKV poses, besides the immediate effects of severe outbreaks and acute infections, is its long-term effect on patients' quality of life. CHIKV infections have a relatively low mortality rate but often result in severe arthralgia and myalgia amongst patients¹⁰, as well as long-term symptoms akin to rheumatoid arthritis that last for months, or in some cases years, post-infection. In Latin America, DENV is still responsible for the vast majority of arboviral disease incidence and mortality. However, based on CHIKV infections in 2014 in the region, analyses have estimated that approximately 50% of all patients who were infected would subsequently develop chronic inflammatory rheumatism¹¹. Following the emergence of ZIKV mid-2015, there were approximately 1.5 million confirmed cases of all three arboviruses by the following year¹².

ZIKV is the least well understood out of the three arboviruses. The virus was first isolated in 1947 from a sentinel monkey in Uganda, with sporadic infections across Africa and Asia and eventually causing the major outbreaks in the Yap State in 2007¹³ and subsequently in French Polynesia in 2013¹⁴. Infections by ZIKV were reported as generally mild, with minimal complications and fatalities, until the major outbreak in 2015 where the unprecedented spread of the disease across the Americas were associated with far more severe disease pathogenicity and neurological complications¹⁵. Out of all flaviviruses, ZIKV is the only one known to cause congenital infections amongst humans, resulting in microcephaly and birth defects in babies following symptomatic ZIKV infections in the mother¹⁶.

Disease control and international travel

The dramatic geographical expansion of the

arboviruses has been associated with the emergence of global trends driven by population and economic growth. Characteristic globalisation, urbanisation and international mobility following such developments have enabled the rapid cross-border travel of people, animals and goods, along with the exchange of various strains of DENV and importation of CHIKV and ZIKV. Travel-associated cases have been reported across the USA and in 16 countries in Europe, with Croatia, France and Portugal experiencing autochthonous dengue transmission⁵. In Malaysia, the Klang Valley is subject to high rates of population movement between other states across the country. Frequent population movement would contribute to disease incidence through the transport of different DENV serotypes and changing susceptibility of the resident population. Furthermore, continuous expansion into new habitats for development and dwelling through activities such as deforestation have resulted in changes in land cover, increasing human exposure to mosquitoes carrying different DENV strains, as well as the other arboviruses CHIKV and ZIKV¹⁷. Frequent and extensive construction activities occurring in dengue endemic countries may also be a potential contributor to disease transmission¹⁸. In Singapore, a study reported a significantly higher burden of dengue at construction sites, as well as the establishment of a transmission link between specific sites and neighbouring residential housing areas. Construction projects provide conducive environments for mosquito breeding, with large numbers of foreign labour facilitating the cross-border exchange of DENV serotypes between their home countries and place of work¹⁸. The noted geographic variations in dengue incidence are therefore inherently linked to differences in population distribution, rates of urbanisation and population growth and land use especially between rural and urban areas¹⁹.

Despite a variety of interventions and control measures undertaken, dengue epidemics, alongside increasingly frequent reports of CHIKV and sporadic ZIKV outbreaks, have persisted with a rising pattern of incidence and mortality. The understanding of disease burden both in

Malaysia and globally is crucial for the formulation of appropriate health policies for prevention and control of these diseases. Unfortunately, there has been a growing difficulty in quantifying the true global burden of these arbovirus infections, and the ongoing co-circulation of these viruses have posed a significant public health challenge in affected countries. The alarming resurgence of disease in recent years emphasises the need for a more in-depth understanding of the various social and ecological factors that influence the transmission of these arboviruses and the burden of these diseases worldwide. Besides the three arboviruses discussed here, a number of other arboviruses and pathogens may potentially emerge over time, with increasingly common spillover infections and heightened risk of severe epidemics. Integrated and targeted efforts in vector control, and the effective management of these diseases will be crucial in years to come.

Keywords: Arboviruses, Aedes, dengue, Chikungunya, Zika, vector control

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