

## Review Article

# Zika Virus Emergence and Expansion: Lessons Learned from Dengue and Chikungunya May Not Provide All the Answers

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**Abstract.** Following the emergence of Zika in the past decade, there are lessons to be learned from similar emergence events of dengue (DENV) and chikungunya (CHIKV). Specifically, as Zika emerges in the Americas there is a natural tendency to apply the knowledge base of DENV and CHIKV to mitigation and control of a virus with such a similar transmission system. However, there are marked differences that may preclude such broad stroke application of this knowledge base without making potentially faulty assumptions. Herein, Zika virus (ZIKV) transmission is reviewed, and the commonalities among these three arboviruses are discussed. Importantly, the divergence of this particular arbovirus is discussed, as is the need to develop ZIKV-specific knowledge base for mitigation of this disease. Specifically reviewed are 1) emergence and persistence patterns, 2) genetic and phenotypic diversity, 3) vector host range, and finally, 4) alternate transmission routes and added complexity of ZIKV transmission and presentation.

## BACKGROUND

Zika virus (ZIKV) is a newly emergent virus in the western hemisphere, though it was first isolated in Uganda in the 1940s.<sup>1,2</sup> ZIKV transmission is similar to two other important arboviruses: dengue (DENV) and chikungunya (CHIKV). Serological evidence throughout 1950–1980s indicated ZIKV also circulated in human populations in Africa, southeast Asia, and the Indian Ocean. These studies also uncovered a high co-occurrence of neutralizing antibody to DENV and CHIKV.<sup>3–5</sup> The current circulation of ZIKV in Brazil coincides with endemic DENV and recent establishment of CHIKV. Given the similarities of ZIKV transmission system to the DENV and CHIKV systems, we can use the experiences of the two latter viruses to prepare for incursion of the former. However, differences between ZIKV and these other ecologically similar viruses should be appreciated lest application of DENV or CHIKV specific knowledge result in potentially misleading assumptions regarding ZIKV. Below is a review of ZIKV in the context of lessons learned from DENV and CHIKV regarding several factors that describe or influence transmission factors. Specifically reviewed are 1) emergence and persistence patterns, 2) genetic and phenotypic diversity, 3) vector host range, and finally, 4) alternate transmission routes and added complexity of ZIKV transmission and presentation.

**Emergence and persistence patterns.** DENV is a complex of four serotypes that while antigenically related, independently circulate though often together.<sup>6</sup> In these hyperendemic situations, the dynamics of DENV are complicated by the four serotypes where there is potential competition for finite vector populations, as well as complex susceptibility profiles of human populations. Alternation of the dominant serotype (“serotype switching”) is associated with increases in severe DENV disease (hemorrhagic fever and shock syndrome), as reported in Ref. 6. Severe DENV disease is attributed to antibody-dependent enhancement whereby antibodies raised to a primary DENV infection cross-react but sub-neutralize

subsequent infection with heterologous serotype.<sup>6</sup> This means that while rendered unsusceptible to that primary DENV serotype (thus altering dynamics of transmission to that serotype), enhancement may catalyze emergence of heterologous serotypes. Genotypic differences within serotypes may alter the risk of enhancement, indicating that phenotypic heterogeneities as well as genotypic variability are important to DENV transmission<sup>7</sup> (see section Genetic and phenotypic diversity).

In contrast, the dynamics of CHIKV transmission indicate that human susceptibility (and loss thereof) is not complicated by incomplete or enhancing immunological statuses humans. In 2005–2006, CHIKV emerged in East Africa and expanded through the Indian Ocean, most notably on La Reunion where hundreds of thousands were infected.<sup>8</sup> Most recently, CHIKV emerged in the Americas where the human population was almost completely susceptible,<sup>2</sup> infecting over a million people in a relatively short time. Infection with CHIKV is presumed to confer lifelong immunity meaning that all individuals infected with CHIKV become immune and are unavailable for future infections. Thus, recurring CHIKV outbreaks are functionally related to the turnover rate of susceptible humans (in addition to reintroduction rates).

Similar to both DENV and CHIKV, reports of ZIKV outbreaks were sporadic until the latter part of the twentieth century, with an increase in the last decade especially. The largest outbreak recorded occurred in 2007 on the Island of Yap where over 5,000 human infections were estimated.<sup>9</sup> Since, there have been additional outbreaks (Figure 1) and it appears that ZIKV infections convey lasting immunity, like CHIKV. However, as ZIKV is a member of the Japanese encephalitis virus (JEV) serocomplex, where it closely groups with Spondweni virus.<sup>10</sup> Within the JEV group, there may be some cross-reactivity and potential cross-neutralization to other members of the JEV group.<sup>11</sup> There is conflicting information regarding the potential for ZIKV cross-reactivity specifically with DENV. Some studies have demonstrated cross-reaction with DENV,<sup>12,13</sup> while others demonstrated that enzyme-linked immunosorbent assay for IgM and IgG in ZIKV acute and convalescent serum samples do not cross-react with DENV.<sup>14–16</sup> Thus, there is still need for clarification of clinical protection and immunogenic cross-reactivity of ZIKV, DENV, and potentially other JEV group members.

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100% saliva infectious after 14 days postexposure.<sup>21,22</sup> However, Senegalese strains of *Ae. aegypti* showed no ability to transmit ZIKV of the same genotype.<sup>23</sup>

Relatedly, the documented vector host range associated with ZIKV outbreaks is more diverse than that of DENV or CHIKV. First isolated from a forest mosquito (*Aedes africanus*), ZIKV is transmitted efficiently by nine *Aedes* mosquito species as well as *Anopheles* species.<sup>19</sup> The relative role of these mosquitoes in future emergence and persistence needs further study. The continued expansion of *Ae. albopictus* does open the possibility of transmission in more temperate regions. In addition, several of these ZIKV competent mosquitoes are more associated with sylvatic cycles rather than the urban and peri-urban ecologies of *Ae. aegypti* and *Ae. albopictus*. Could this indicate that there are similarly competent forest-associated vectors in South and Central America? If that is the case, there is potential for establishment of a reservoir system, as ZIKV-specific antibody has been detected in non-human primates as well as rodents.<sup>24,25</sup> Though virus has not been isolated from rodents or non-human primates (NHP) in recent surveys, the virus was originally identified from a sentinel monkey, indicating NHP could potentially support sylvatic transmission.

**Alternate routes and added complexity.** While many lessons learned can inform hypotheses regarding ZIKV transmission, there are the lessons that remain unanswered for all three arboviruses. Most notable is the distribution of asymptomatic cases and thus the total force of infection within human populations. High rates of subclinical disease lead to underestimates in total DENV incidence, though the actual proportion varies considerably.<sup>26</sup> CHIKV was thought to have a higher presentation rate compared with DENV, but recent reports have estimated as much as 47% of infections are asymptomatic.<sup>27</sup> ZIKV asymptomatic rates were estimated to be relatively high during the Yap Island outbreak,<sup>9</sup> though in subsequent outbreaks these were not reported. Until there is comprehensive knowledge of asymptomatic rates—not only the prevalence of, but also mechanisms behind them—assessments of total transmission will be underestimates.

As DENV and CHIKV are already established in the areas where ZIKV is reported and/or has the potential to establish, there is a high likelihood for co-circulation. There remain questions regarding the interplay among arboviruses with such similar ecologies. Arbovirus coinfection in mosquitoes do not often result in dually infectious mosquitoes, though there are few exceptions.<sup>28</sup> Since DENV, CHIKV, and ZIKV share the same urban vectors in areas such as the Americas (*Ae. aegypti* and *Ae. albopictus*), competitive dynamics are likely as they co-circulate in a finite vector population. This may alter epidemic patterns of already-established viruses such as DENV or of the future (re)emergence of other viruses like CHIKV, yellow fever, or Spondweni viruses.

While DENV and CHIKV are primarily transmitted through the bite of infectious mosquitoes, there are alternative means of human-to-human ZIKV transmission. ZIKV has been detected in urine and saliva, and there are case reports of sexual and perinatal transmission.<sup>29–31</sup> Though isolated incidents, alternate means of transmission (and thus potential virus perpetuation) do suggest that the factors involved in emergence potential of ZIKV may be more complex than the DENV and CHIKV transmission systems. Further, recent surges in microcephaly incidence in Brazil has coincided with the emergence

of ZIKV, over 1,700 cases as of the writing of this article.<sup>20</sup> While the epidemiological observations certainly suggest an association, causation has not been definitely established: ZIKV RNA has been confirmed in only one case, though testing continues.<sup>20</sup> It is notable that in no other previous ZIKV outbreak has there been an association made with increases in microcephaly. However, the reports are compelling and the Brazilian government has issued a warning suggesting that women wait to get pregnant. In light of the potential sexual transmission, campaigns to help pregnant women or women trying to get pregnant avoid mosquitoes should also include their partners, as well as for men seeking to donate or bank semen. Regardless, the education infrastructure is likely to have a challenge in the years to come when this comparatively larger population of children with special needs looks to enter the education system. Thus, the social implications of ZIKV look to be more long term and multifaceted than either DENV or CHIKV.

## CONCLUSIONS

Following the emergence of CHIKV in the Americas, a spate of cases in Brazil did not clinically fit the definition of either DENV or CHIKV, prompting officials to molecularly investigate ZIKV.<sup>28</sup> ZIKV was confirmed in seven of eight patients and determined to be of the Asian lineage, which has also been circulating in the Philippines since 2012.<sup>14,28</sup> This was the first cases of autochthonous transmission of ZIKV in the region, and cases have been reported now in several Central and South American countries.<sup>19</sup> There have been traveler-associated ZIKV cases, most recently originating from this Brazilian outbreak.<sup>32,33</sup> According to the U.S. Centers for Disease Control, there were nearly 2,300 cases of returned traveler-associated CHIKV in 2014 and over 550 in 2015 as of the writing of this review. As ZIKV continues to expand throughout the Americas, it presents another likely source of travel medicine woes.

The knowledge base of ZIKV is considerably smaller than that of DENV and even CHIKV, which itself lags behind DENV. Given the similarities among the three arboviruses and the likely vectors to be associated with autochthonous transmission, it is natural and necessary that we look back at the DENV and CHIKV experiences. However, there are a number of differences that indicate that these experiences may not provide a complete list of answers, and we should take care to investigate the important questions regarding transmission and not fall into patterns of assumption. Going forward, there needs to be thoughtful investigation of 1) the interplay of ZIKV and other circulating arboviruses on human infectivity and immunological cross-reactivity; 2) the capacity for alternate transmission routes to alter expectation of ZIKV emergence, expansion, and/or persistence; 3) ZIKV-specific dynamics in known and potentially competent vector species; and 4) the capacity for a reservoir system and/or sylvatic transmission cycle. We should recognize that these and other co-circulating arboviruses cannot be studied in isolation if we are to fully realize comprehensive approaches to transmission control and disease mitigation.

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