

## Arboviruses and Their Vectors

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Arthropod-transmitted viruses (arboviruses) pose important public health challenges worldwide, and continue to do so even while the world is contending with the 2019 coronavirus disease (COVID-19) pandemic. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spread by contact with respiratory droplets from infected individuals. Arboviruses pose a different threat to humanity because of their efficient transmission by our formidable health adversary, the mosquito. There is no evidence that mosquitoes are vectors for SARS-CoV-2 or the two structurally related viruses causing SARS or Middle East respiratory syndrome. There are >500 recognized arboviruses worldwide, 150 of which are known to cause human disease.<sup>1</sup> This figure may only represent <1% of all arboviruses, as most are zoonotic infections among hosts other than humans.<sup>1</sup> Worldwide, the most prevalent arboviral diseases per year are dengue fever (DENV; 96 million cases), chikungunya virus (CHIKV; 693,000 cases), Zika virus (ZIKV; 500,000 cases), yellow fever (130,000 cases), Japanese encephalitis (42,500 cases), and West Nile virus (2,588 cases).<sup>2</sup> Other emergent or reemergent arboviral diseases are Eastern equine encephalitis, St Louis encephalitis, La Crosse encephalitis, Rift Valley fever, Spondweni, Mayaro, Usutu, O'nyong-nyong, and Sindbis. As such, arboviral diseases also must remain a clinical focus for physicians beyond the overwhelming concern for COVID-19. In fact, these diseases may complicate efforts to identify COVID-19, especially in underresourced environments, as they share some clinical and laboratory features. This is exemplified by a recent report of a patient in Thailand who was initially diagnosed as having dengue fever, but was later confirmed to be co-infected with SARS-CoV-2.<sup>3</sup> Concurrent outbreaks of influenza and dengue viruses also have been reported to cause challenges in underlying pathogen identification and delayed recognition of outbreaks of either of the diseases in the community.<sup>4</sup>

DENV, CHIKV, and ZIKV viruses are of current concern because of rising incidence, expanding geographic range, clinically important disease spectrum, and public health burden. These viruses share epidemiology, transmission pathways, and clinical expressions, although their complications vary. The clinical signs associated with infection from these arboviruses are often

inapparent, mild, or nonspecific, but they may include serious complications. Definitive diagnoses of DENV, CHIKV, and ZIKV may be made with enzyme-linked immunosorbent assay or reverse transcriptase-polymerase chain reaction, but these tests may not be readily available in many underresourced laboratory settings.

### DENV

DENV is a single-stranded, lipid-enveloped, nonsegmented RNA *Flavivirus* of the *Flaviviridae* family.<sup>5</sup> More than half of the viruses in the genus *Flavivirus* cause human diseases, including yellow fever, West Nile, Japanese encephalitis, and St Louis encephalitis viruses. DENV is the most prevalent and rapidly spreading arbovirus, with community transmission occurring in 128 countries, thereby creating risks for 4 billion people.<sup>6</sup> There are 390 million DENV infections worldwide annually, including 96 million clinical cases, 500,000 dengue hemorrhagic fever (DHF) cases, and 22,000 deaths, mostly children 5 years of age and younger.<sup>6</sup> COVID-19 arrived during a major DENV epidemic. There were >3.1 million cases in the Americas alone in 2019, and >1.6 million cases in the first 21 weeks of 2020.<sup>7</sup>

Dengue infections are caused by four serotypes (DENV-1 to DENV-4), and infection from one serotype confers lifelong immunity for that serotype but only limited protection for other serotypes (and for only a few months after infection). A fifth variant, DENV-5, was isolated in October 2013.<sup>8</sup> Half of all DENV infections are asymptomatic, but all DENV serotypes may cause febrile illness, sudden-onset skin rash, myalgia, headache, and vomiting.<sup>9</sup> The complications of DENV include DHF and dengue shock syndrome. Without proper treatment, 1% to 20% of DHF cases lead to death, whereas with treatment, the case fatality rate is <1%.<sup>6</sup> The risk of DHF may increase up to 15 to 500 times following a secondary infection with a different serotype.<sup>10</sup> DHF, however, is typically observed in only a small percentage of secondary infections and is rare in primary DENV infections.<sup>11</sup> There is evidence of cross-immunity between DENV and other *Flaviviruses*, including ZIKV<sup>12</sup> and yellow fever,<sup>13</sup> although these immunologic patterns are poorly understood.

### CHIKV

First identified in Tanzania in 1952, CHIKV is an enveloped plus-strand RNA *Alphavirus*.<sup>14</sup> The word *chikungunya* in the Kimakonde language means “that which bends up,” which may have derived from the hunched posture among infected individuals with severe joint and arthritic pain.<sup>15</sup> CHIKV is of the *Togaviridae* family, which includes O'nyong-nyong, Mayaro, Ross River, and Semliki Forest viruses. Outbreaks in 2004 in Africa and Asia were followed by outbreaks in the Americas in 2015.<sup>14</sup> Local transmission of CHIKV was described in the United States in 2014 and has been identified in >60 countries in Asia, Africa, Europe, and the Americas.<sup>14</sup> In contrast to DENV and ZIKV, most people infected with CHIKV are symptomatic.<sup>15</sup> CHIKV causes severe arthralgia and

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persistent rheumatic symptoms.<sup>15</sup> Symptoms may last months to years, especially in those 35 years of age and older.<sup>16</sup> Other complications include prolonged arthritis, meningoencephalitis, nephritis, retinitis, uveitis, myelitis, cranial nerve palsies, and acute encephalopathy.<sup>17</sup>

## ZIKV

ZIKV is a single-stranded enveloped RNA *Flavivirus* of the *Flaviviridae* family. First identified in Uganda in 1947, ZIKV expanded into the South Pacific region and the Americas, with 48 countries reporting active ZIKV by 2017 and 86 by 2019.<sup>18,19</sup> Like other arboviruses, ZIKV infection confers lifelong immunity to reinfection.<sup>20</sup> Although 60% to 80% of infected individuals are asymptomatic,<sup>21</sup> ZIKV may cause fever, rash, conjunctivitis, arthralgia, myalgia, headache, dysesthesia, retroorbital pain, asthenia, and arthritis.<sup>20,22</sup> ZIKV infection has also been linked to Guillain-Barré syndrome.<sup>23</sup>

Other horizontal (eg, sexual, blood transfusions) and vertical (mother-to-fetus) transmissions have been reported for ZIKV.<sup>19</sup> Sexual transmission of ZIKV has been reported up to 44 days after onset of symptoms, and the viral RNA may remain in semen for 180 days after symptom onset.<sup>24,25</sup> An estimated 5% to 15% of women infected with ZIKV during pregnancy give birth to infants with congenital abnormalities.<sup>23</sup> Congenital Zika syndrome encompasses a range of disorders, including microcephaly, encephalitis, craniofacial disproportion, cerebral palsy, hearing loss, brainstem dysfunctions, spasticity, joint deformities, clubfoot, and developmental and inflammatory ocular diseases.<sup>20,22</sup>

## Vectors

*Aedes aegypti* are small, dark mosquitoes with white markings on their legs. They have four life stages (egg, larva, pupa, adult), a process that takes 8 to 10 days, depending on temperature, food availability, and larval density.<sup>26</sup> Males may mate frequently throughout their lifetimes, but only one sperm dose is needed by females to produce numerous batches of eggs. Females lay 100 eggs at a time and need as little as a bottle cap full of water to lay eggs, which may hatch and develop into adults in 1 week.<sup>26</sup> The eggs are durable, capable of remaining viable after freezing, and surviving in desiccated settings for >1 year.<sup>27</sup> Males survive 2 to 3 weeks in the field, whereas females may survive 4 to 5 weeks.<sup>28</sup>

Male mosquitoes do not bite humans, but females are voracious daytime feeders seeking blood for protein to make eggs. *A. aegypti* have a strong preference for human blood, whereas *A. albopictus* are less discriminate, feeding on both humans and animals.<sup>29</sup> *A. aegypti* may ingest 3 to 4  $\mu$ L blood, twice its body weight, and may become infected with an arbovirus after feeding on a viremic human. Once infected, *A. aegypti* remains infected for life.<sup>30</sup> Viruses in *A. aegypti* saliva may be transmitted to humans by bites from infected females. *A. aegypti* are capable of transmitting >1 arbovirus during a single feeding episode.<sup>31</sup> Females may take multiple blood meals to complete the 2- to

8-day gonotrophic cycle that begins with blood meals and ends with egg-laying.<sup>32</sup>

Once a forest-dwelling zoophilic mosquito, *A. aegypti* adapted into an anthropophilic highly domesticated species, preferring urban areas in and around households, whereas *A. albopictus* prefer rural, suburban, and urban settings.<sup>28,29</sup> *A. aegypti* rarely disperse beyond 30 to 40 m of the household where they developed as larvae and fly a total of 40 to 80 m throughout their lifetimes.<sup>33,34</sup> Ideal larval habitats for *A. aegypti* are dark-colored containers with stagnant water and organic material in shaded areas around houses.<sup>35</sup> Productive container types include flowerpots, tires, vases, buckets, cans, rain gutters, fountains, bottles, and birdbaths.<sup>35</sup> Single containers may be extremely productive; one septic tank in Puerto Rico produced >1500 *A. aegypti* per day.<sup>36</sup> *A. albopictus* can live in a broader temperature range and cooler temperatures than *A. aegypti*.<sup>37</sup> *A. aegypti* prefer to rest inside houses on walls, in closets, or underneath furniture, whereas *A. albopictus* generally rest outdoors. Stay-at-home COVID-19 requirements may increase household *A. aegypti* bites, as there is a demonstrated association between household crowding and arbovirus infections.<sup>38,39</sup> Upon arrival to new areas, the invasive *A. aegypti* and *A. albopictus* have demonstrated an ability to replace resident mosquito populations via competitive exclusion.<sup>40</sup>

Climate change, urbanization, migration, human behavior, and ecosystem alterations are among the myriad factors influencing the geographic spread of *Aedes* spp. and their viruses. In 2014, 54% of people lived in urban areas worldwide, which is expected to increase to 66% by 2050.<sup>41</sup> Greater human population densities provide more feeding opportunities for *A. aegypti*. Global temperatures are expected to increase 2°C to 4.5°C by 2100, potentially exposing an additional 2 billion people to arboviruses, including higher-latitude US states.<sup>42</sup> More than 60% of the world's population will be at risk for DENV by 2080.<sup>43</sup>

Approximately 6.01 billion people live in areas suitable for *A. aegypti* transmission and 6.33 billion live in areas suitable for *A. albopictus*.<sup>44,45</sup> To date, *A. aegypti* has been frequently, albeit sporadically, reported in California, Texas, Florida, Louisiana, Mississippi, Georgia, and Arizona.<sup>46</sup> The potential range of *A. aegypti* in the United States is enormous, encompassing the entire US southern tier.<sup>47</sup> Other *Aedes* spp. may spread arboviruses in Africa, Asia, and the Pacific Rim.<sup>48</sup> For example, ZIKV has been identified in 16 different *Aedes* species.<sup>18</sup> Fewer *A. aegypti* or *A. albopictus* are required to cause local arbovirus transmission in immunologically naïve communities where herd immunity is low or nonexistent and ambient temperature is high.<sup>44</sup>

## Vector Control

Other than for DENV, yellow fever, and Japanese encephalitis viruses, there are no commercially available vaccines for arboviruses. The DENV vaccine has been licensed in >20 countries including the United States, but has not been incorporated into any national program because of difficult logistical requirements for prevaccination.<sup>49</sup> As such, vector control and human behavior

modification, to maintain mosquitoes below the local transmission density threshold, are the most widely used preventive strategies.<sup>44</sup>

Integrated vector management, promoted by the World Health Organization, recommends a combination of vector control strategies that target different stages of the mosquito life cycle and may be biological, chemical, or environmental.<sup>50</sup> Immature mosquito control strategies include larval source-reduction campaigns and treating water containers with bleach, insecticides, copepods, larvivorous fish, or entomopathogenic fungi.<sup>51</sup> Adult mosquito control strategies target different mosquito behaviors such as mating (eg, release of insects with dominant lethality), sugar feeding (eg, toxic sugar traps), blood feeding (eg, personal protection such as repellents, protective clothing, bed nets), resting (eg, indoor residual spraying), or egg-laying (eg, lethal ovitraps).<sup>51</sup> Other vector management efforts include mass deployment of gravid ovitraps or releasing *A. aegypti* transected with the endosymbiont bacterium *Wolbachia*.<sup>52,53</sup> *A. aegypti* have developed resistance to commonly used insecticides, including pyrethroids.<sup>54</sup>

Diversion of support to combat SARS-CoV-2 may compromise mosquito control programs. For example, Sri Lanka; Regina, Canada; and East Baton Rouge, Louisiana temporarily suspended mosquito larviciding programs to increase support for combating SARS-CoV-2.<sup>55-57</sup> A poll by the National Association of County and City Health Officials demonstrated that 40% of vector control programs had moderate reductions to complete shutdowns of vector control programs because of the COVID-19 pandemic, with large portions of staff being reassigned to the pandemic response.<sup>58</sup> Proactive community-wide and household measures must be taken to eliminate domestic mosquito breeding sites. Vector control measures should be implemented and practiced alongside COVID-19 prevention strategies such as handwashing, cleaning surfaces, and social distancing.

## Conclusions

With global warming, the mosquito's range will continue to expand north and south into areas that were previously free of mosquito-borne diseases, including higher altitudes.<sup>2,45</sup> The rapid emergences of DENV, CHIKV, and ZIKV underscore the reality that new pathogens causing dangerous epidemics may emerge at any time. The introduction of West Nile virus in North America and its rapid spread throughout the western hemisphere provide a vivid example of the ability of an emerging arbovirus to cause a significant public health impact in a new environment. Other arboviruses, including Mayaro, Nipah, and Spondweni may be emerging threats.<sup>59,60</sup> Recent outbreaks of yellow fever in Brazil and Africa foreshadow the reemergence of previously controlled diseases.<sup>61</sup> Until safe, effective, and affordable vaccines are available worldwide, robust surveillance programs and aggressive vector control efforts are the best methods for limiting their spread.

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