



Perspective

Zika Virus in the Americas — Yet Another Arbovirus Threat

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The explosive pandemic of Zika virus infection occurring throughout South America, Central America, and the Caribbean (see map) and potentially threatening the United States is the most

recent of four unexpected arrivals of important arthropod-borne viral diseases in the Western Hemisphere over the past 20 years. It follows dengue, which entered this hemisphere stealthily over decades and then more aggressively in the 1990s; West Nile virus, which emerged in 1999; and chikungunya, which emerged in 2013. Are the successive migrations of these viruses unrelated, or do they reflect important new patterns of disease emergence? Furthermore, are there secondary health consequences of this arbovirus pandemic that set it apart from others?

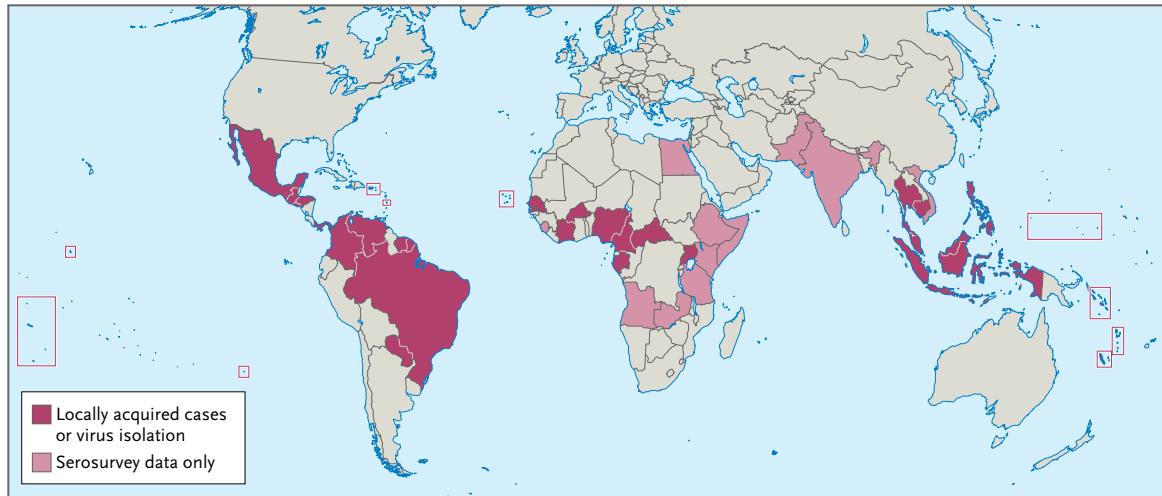
“Arbovirus” is a descriptive term applied to hundreds of predominantly RNA viruses that are transmitted by arthropods, notably mosquitoes and ticks. Arboviruses are often maintained in

complex cycles involving vertebrates such as mammals or birds and blood-feeding vectors. Until recently, only a few arboviruses had caused clinically significant human diseases, including mosquito-borne alphaviruses such as chikungunya and flaviviruses such as dengue and West Nile. The most historically important of these is yellow fever virus, the first recognized viral cause of deadly epidemic hemorrhagic fever.

Zika, which was discovered incidentally in Uganda in 1947 in the course of mosquito and primate surveillance,¹ had until now remained an obscure virus confined to a narrow equatorial belt running across Africa and into Asia. The virus circulated predominantly in wild primates and arboreal mosquitoes such as *Aedes africanus* and rarely caused recog-

nized “spillover” infections in humans, even in highly enzootic areas.² Its current explosive pandemic reemergence is therefore truly remarkable.³ Decades ago, African researchers noted that aedes-transmitted Zika epizootics inexplicably tended to follow aedes-transmitted chikungunya epizootics and epidemics. An analogous pattern began in 2013, when chikungunya spread pandemically from west to east, and Zika later followed. Zika has now circled the globe, arriving not only in the Americas but also, in September, in the country of Cape Verde in West Africa, near its presumed ancient ancestral home.

With the exception of West Nile virus, which is predominantly spread by culex-species mosquitoes, the arboviruses that recently reached the Western Hemisphere have been transmitted by aedes mosquitoes, especially the yellow fever vector mosquito *A. aegypti*. These viruses started to emerge millennia ago, when North African villagers began to store water in



Countries with Past or Current Evidence of Zika Virus Transmission (as of December 2015).

For countries with serosurvey data only, evidence of Zika virus transmission is derived from studies that detected Zika virus antibodies in healthy people. Outlined areas, all with locally acquired cases or virus isolation, include Cape Verde, Cook Islands, Easter Island, Federated States of Micronesia, French Polynesia, Martinique, New Caledonia, Puerto Rico, Solomon Islands, and Vanuatu. Data are from the Centers for Disease Control and Prevention (<http://www.cdc.gov/zika>).

their dwellings. Arboreal *A. aegypti* then adapted to deposit their eggs in domestic water-containing vessels and to feed on humans, which led to adaptation of arboviral viruses to infect humans. The yellow fever, dengue, and chikungunya viruses evolved entirely new maintenance cycles of human–*A. aegypti*–human transmission.⁴ Now, 5000 years later, the worst effects of this evolutionary cascade are being seen in the repeated emergence of arboviruses into new ecosystems involving humans. Moreover, arboviruses transmitted by different mosquitoes have, in parallel, adapted to humans' domestic animals, such as horses in the case of Venezuelan equine encephalitis and pigs in the case of Japanese encephalitis virus, or to vertebrate hosts and non-aedes mosquitoes found in areas of human habitation, as West Nile virus did. The possibility that Zika may yet adapt to transmission by *A. albopictus*, a much more widely distributed mosquito found in at least 32 states in the United States, is cause for concern.

Through early epidemiologic surveillance and human challenge studies, Zika was characterized as a mild or inapparent dengue-like disease with fever, muscle aches, eye pain, prostration, and maculopapular rash. In more than 60 years of observation, Zika has not been noted to cause hemorrhagic fever or death. There is in vitro evidence that Zika virus mediates antibody-dependent enhancement of infection, a phenomenon observed in dengue hemorrhagic fever; however, the clinical significance of that finding is uncertain.

The ongoing pandemic confirms that Zika is predominantly a mild or asymptomatic dengue-like disease. However, data from French Polynesia documented a concomitant epidemic of 73 cases of Guillain-Barré syndrome and other neurologic conditions in a population of approximately 270,000, which may represent complications of Zika. Of greater concern is the explosive Brazilian epidemic of microcephaly, manifested by an apparent 20-fold in-

crease in incidence from 2014 to 2015, which some public health officials believe is caused by Zika virus infections in pregnant women. Although no other flavivirus is known to have teratogenic effects, the microcephaly epidemic has not yet been linked to any other cause, such as increased diagnosis or reporting, increased ultrasound examinations of pregnant women, or other infectious or environmental agents. Despite the lack of definitive proof of any causal relationship,⁵ some health authorities in afflicted regions are recommending that pregnant women take meticulous precautions to avoid mosquito bites and even to delay pregnancy. It is critically important to confirm or dispel a causal link between Zika infection of pregnant women and the occurrence of microcephaly by doing intensive investigative research, including careful case-control and other epidemiologic studies as well as attempts to duplicate this phenomenon in animal models.

In a “pure” Zika epidemic, a

diagnosis can be made reliably on clinical grounds. Unfortunately, the fact that dengue and chikungunya, which result in similar clinical pictures, have both been epidemic in the Americas confounds clinical diagnoses. Specific tests for dengue and chikungunya are not always available, and commercial tests for Zika have not yet been developed. Moreover, because Zika is closely related to dengue, serologic samples may cross-react in tests for either virus. Gene-detection tests such as the polymerase-chain-reaction assay can reliably distinguish the three viruses, but Zika-specific tests are not yet widely available.

The mainstays of management are bed rest and supportive care. When multiple arboviruses are cocirculating, specific viral diagnosis, if available, can be important in anticipating, preventing, and managing complications. For example, in dengue, aspirin use should be avoided and patients should be monitored for a rising hematocrit predictive of impending hemorrhagic fever, so that potentially lifesaving treatment can be instituted promptly. Patients with chikungunya virus infection should be monitored and treated for acute arthralgias and postinfectious chronic arthritis.

There are no Zika vaccines in advanced development, although a number of existing flavivirus vaccine platforms could presumably be adapted, including flavivirus chimera or glycoprotein subunit technologies. Zika vaccines would, however, face the same problem as vaccines for chikungunya,⁴ West Nile, St. Louis encephalitis, and other arboviruses: since epidemics appear sporadically and unpredictably, preemptively vaccinating large populations in anticipation of outbreaks may be prohibitively expensive and

not cost-effective, yet vaccine stockpiling followed by rapid deployment may be too slow to counter sudden explosive epidemics. Although yellow fever has historically been prevented entirely by aggressive mosquito control, in the modern era vector control has been problematic because of expense, logistics, public resistance, and problems posed by inner-city crowding and poor sanitation. Among the best preventive measures against Zika virus are house screens, air-conditioning, and removal of yard and household debris and containers that provide mosquito-breeding sites, luxuries often unavailable to impoverished residents of crowded urban locales where such epidemics hit hardest.

With its recent appearance in Puerto Rico, Zika virus forces us to confront a potential new disease-emergence phenomenon: pandemic expansion of multiple, heretofore relatively unimportant arboviruses previously restricted to remote ecologic niches. To respond, we urgently need research on these viruses and the ecologic, entomologic, and host determinants of viral maintenance and emergence. Also needed are better public health strategies to control arboviral spread, including vaccine platforms for flaviviruses, alphaviruses, and other arbovirus groups that can be quickly modified to express immunogenic antigens of newly emerging viruses. With respect to treatment, the arbovirus pandemics suggest that the one-bug-one-drug approach is inadequate; broad-spectrum antiviral drugs effective against whole classes of viruses are urgently needed.

As was realized more than 50 years ago, when enzootic Zika virus spread was linked to human activity, arboviruses continually

evolve and adapt within ecologic niches that are increasingly being perturbed by humans. Zika is still a pandemic in progress, and many important questions about it, such as that of teratogenicity, remain to be answered. Yet it has already reinforced one important lesson: in our human-dominated world, urban crowding, constant international travel, and other human behaviors combined with human-caused microperturbations in ecologic balance can cause innumerable slumbering infectious agents to emerge unexpectedly. In response, we clearly need to up our game with broad and integrated research that expands understanding of the complex ecosystems in which agents of future pandemics are aggressively evolving.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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