The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 18, 2016

Zika Virus in the Americas — Yet Another Arbovirus Threat

Anthony S. Fauci, M.D., and David M. Morens, M.D.

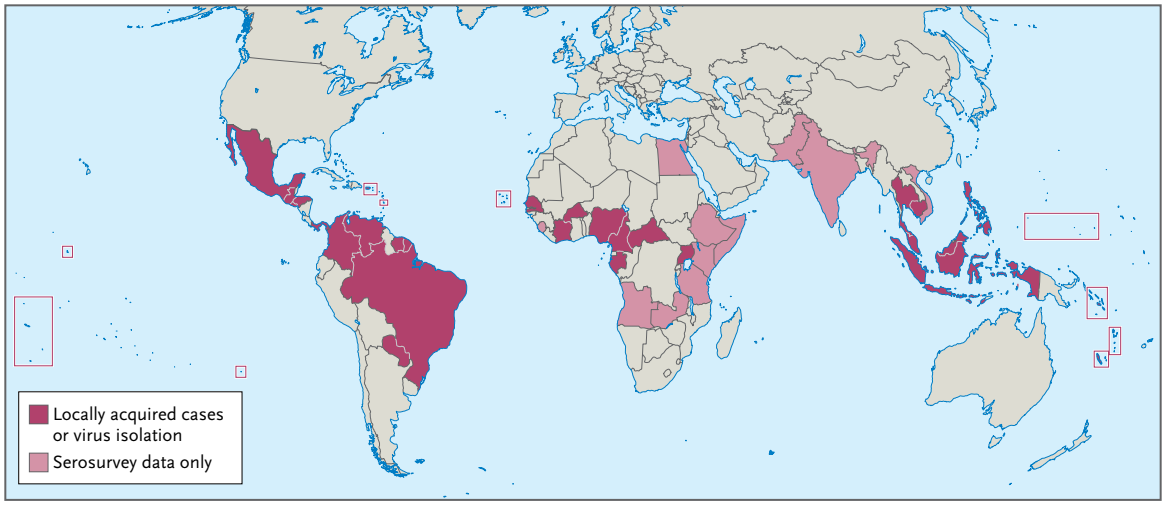
The explosive pandemic of Zika virus infection occurring throughout South America, Central America, and the Caribbean (see map) and potentially threatening the United States is the most recent of four unexpected arrivals of important arthropod-borne viral diseases in the Western Hemisphere over the past 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 recognized "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

The New England Journal of Medicine
Downloaded from nejm.org at NIH Libary on January 3, 2018. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.



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).

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 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 arboreal 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 increase 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 impor-

The New England Journal of Medicine
Downloaded from nejm.org at NIH Libary on January 3, 2018. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.

tant 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.

From the National Institute of Allergy and Infectious Diseases, Bethesda, MD.

This article was published on January 13, 2016, at NEJM.org.

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg 1952;46:509-20.
2. Pierson TC, Diamond MS. Flaviviruses. In: Knipe DM, Howley PM, Cohen IC, et al., eds. Fields virology. 6th ed. Vol. 1. Philadelphia: Wolters Kluwer, 2014:746-94.
3. Marcondes CB, Ximenes MF. Zika virus in Brazil and the danger of infestation by *Aedes* (*Stegomyia*) mosquitoes. Rev Soc Bras

The New England Journal of Medicine
Downloaded from nejm.org at NIH Libary on January 3, 2018. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.

Med Trop 2015 December 22 (Epub ahead of print).
4. Morens DM, Fauci AS. Chikungunya at the door — déjà vu all over again? N Engl J Med 2014;371:885-7.
5. European Centre for Disease Prevention and Control. Microcephaly in Brazil potentially linked to the Zika virus epidemic: ECDC assesses the risk. Solna, Sweden: European Centre for Disease Prevention and Control, November 25, 2015 (http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=1329&List=8db7286c-fe2d-476c-9133-18ff4cb1b568&Source=http%3A%2F%2Fecdc.europa.eu%2Fen%2FPages%2Fhome.aspx).
DOI: 10.1056/NEJMp1600297
Copyright © 2016 Massachusetts Medical Society.

How Employers Are Responding to the ACA

Robert Galvin, M.D.

The Affordable Care Act (ACA) changed employers' role in the U.S. health care system. Employer-sponsored insurance, a long-standing system component, provides health coverage for more 160 million Americans. While preserving the employer-based system, the ACA fundamentally altered it by making the provision of health benefits mandatory rather than voluntary for employers with more than 50 employees and establishing minimum criteria for affordability and coverage. In addition, a "play or pay" model was created, providing employers with an exit: employees would no longer become uninsured if their employers dropped benefits but could instead purchase guaranteed and potentially subsidized insurance through public exchanges.

Two financial milestones are leading employers to evaluate whether they want to play or pay. In 2015, employers with more than 100 employees became subject to a shared-responsibility penalty for coverage that didn't meet federal standards; further down the road, a 40% excise tax on coverage over a maximum dollar value (the so-called Cadillac tax) is due to go into effect (implementation was originally set for 2018, but Congress recently voted to delay it by 2 years). Although it's still early in the game, employers are making key decisions that affect patients, health care providers, and insurers.

So far, almost all employers have continued to "play." Given that sponsoring health benefits is not a core business function, why are so few firms ceasing to do so? The biggest reason is that there is no cost advantage to discontinuing health coverage. The "simple math" that a $2,000 fine is less than the $10,000 average per-employee cost of coverage is complicated by the tax deductibility of employers' health care contributions. The increase in non–tax-deductible salaries that would be needed to keep projected health care costs from damaging employee recruitment and retention efforts exceeds the savings an employer could expect from dropping health care coverage.

A second reason is that the business community is skeptical that the government can manage large social programs efficiently and therefore expects the penalties to increase. And a third, underappreciated reason is that growth in health care costs has slowed substantially over the past several years, so employers don't feel compelled to make a change.

Private insurance exchanges have been promoted as a nongovernmental exit option. These products allow firms to outsource the design and delivery of health benefits. They differ from the public exchanges in that employers can continue to be regulated under the Employee Retirement Income Security Act (ERISA) and remain self-insured — which means lower costs and less exposure to regulation — but employees receive no means-based subsidies. Despite aggressive marketing by such exchanges, very few companies have adopted this strategy for active employees, according to the Employee Benefit Research Institute. Most of the big-name companies that have pursued this route compete in low-wage labor markets in which offering health benefits is not considered essential to finding employees; their move to private insurance exchanges is not indicative of a broader trend. There's no evidence that private exchanges can control costs any better than employers are doing on their own.

Employers will face a second financial milestone if the Cadillac tax becomes effective in 2020. The provision, levying a 40% nondeductible tax on the value of health benefit plans exceeding a specified amount (currently $10,200 annually for individuals), has captured the attention of chief executives, who are focusing more on health care than they have

The New England Journal of Medicine
Downloaded from nejm.org at NIH Libary on January 3, 2018. For personal use only. No other uses without permission.
Copyright © 2016 Massachusetts Medical Society. All rights reserved.