INFECTIOUS DISEASES

An obscure mosquito-borne disease goes global

After racing through Oceania last year, the Zika virus is now spreading in the Americas

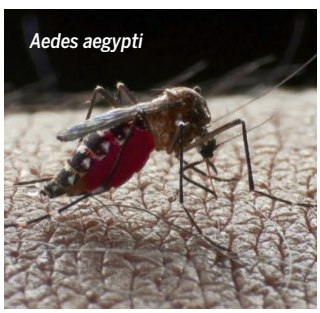
By **Martin Enserink**

Seven years ago, after returning from a field trip to Senegal, medical entomologists Brian Foy and Kevin Kobylinski came down with a serious disease so obscure that no one could find out what it was. The duo, both at Colorado State University, Fort Collins, had a rash, fatigue, headaches, and swollen and painful joints, but they tested negative for known infectious agents.

Both recovered, and they might never have known the cause of their illness if, more than a year later on another African trip, Foy hadn't run into medical entomologist Andrew Haddow, then at the University of Texas Medical Branch in Galveston. In 1947, Haddow's grandfather was working in Africa, where he had helped discover a mosquito-borne virus named Zika. The symptoms it caused seemed to match Foy's. Haddow helped arrange for Foy and Kobylinski to get tested for antibodies. Bingo: They had been infected with Zika.

Now, the oddity that floored Foy and Kobylinski has hit the big time. Eight years ago, after cropping up sporadically in Africa and Asia for half a century, Zika went on a rampage through the Pacific islands. In May of this year it arrived in Brazil, where it has now caused disease in 14 of the country's 27 states; in the past 2 months, cases have also been reported from neighboring Colombia and Suriname. In May and again in October, the Pan American Health Organization warned other countries in the region to prepare for the virus's arrival.

Researchers are only beginning to study the disease and its transmission in earnest. But because the *Aedes* mosquitoes that spread Zika are ubiquitous in urban areas throughout the Americas, it is almost certain that the virus will spread through South and Central America, Mexico, and the Caribbean, says Duane Gubler, who directs the Emerging Infectious Diseases program at National University of Singapore. It will make occasional inroads into the southern United States and southern Europe as well, he predicts.



Gubler feels so sure because two other diseases that are spread by the same species of *Aedes* mosquitoes—most notably *A. aegypti*, the yellow fever mosquito—have expanded in this way. One of the two, dengue, has caused vast epidemics in Latin America the past 40 years. The other, chikungunya, virtually unknown a decade ago, began conquering the Western hemisphere in 2013 (*Science*, 16 May 2014, p. 678), where to date there have been more than 600,000 suspected and confirmed cases in more than 30 countries.

The good news is that Zika has caused no known deaths. Its symptoms resemble those of dengue and chikungunya, but in most patients Zika is milder than those diseases, which both can cause excruciating pain. (Dengue also can progress to dengue hemorrhagic fever, which can be fatal.) But having so many similar viruses circulating at the same time complicates diagnoses and strains public health systems. And Zika's arrival in the Americas raises the question of how many other *Aedes*-borne viruses might emerge. "We have an unholy trinity now—but it could easily grow," Foy says.

Both Zika and dengue are flaviviruses, a genus that also includes yellow fever and the West Nile virus. During the half century after Zika's 1947 discovery—in a rhesus monkey in the Zika Forest near Entebbe, Uganda—fewer than 15 cases were reported, all from Africa and Southeast Asia.

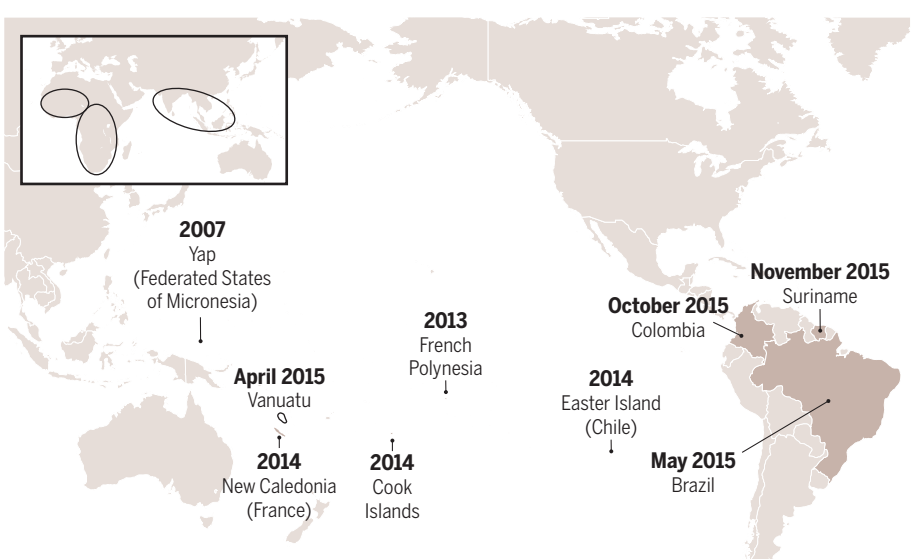
Something changed in 2007, when Zika erupted in a big outbreak in Yap, an island group in the Western Pacific that is part of the Federated States of Micronesia. A 2009 study based on antibody surveys estimated that an astonishing 73% of the population had become infected, although no one died or even was hospitalized.

That was the start of an extended island-hopping tour. Zika infected close to 30,000 people—one-tenth of the population—during an outbreak in French Polynesia in 2013–14; this time, some people did end up in the hospital, and a few developed Guillain-Barré syndrome, a muscle weakness caused by damaged peripheral nerves. That dispelled the notion that Zika is always benign, says Didier Musso of the Institut Louis Malardé on Tahiti, French Polynesia. Infected travelers then probably took the virus to New Caledonia, the Cook Islands, Vanuatu, and Easter Island, where local mosquitoes bit them and started fresh outbreaks.

Although the combination of air travel and large mosquito populations guarantees rapid spread, there may be other transmission routes. After Foy returned home in 2008, his nurse wife, Joy Chilson Foy, contracted Zika

Virus on the move

Zika, which occurred sporadically in Africa and Southeast Asia before 2007 (inset), has caused major outbreaks in Oceania and now has reached the Americas.



as well. Because northern Colorado hosts no mosquitoes that can act as Zika vectors, and because Foy had prostatitis and blood in his semen at the time, the most likely explanation is sexual transmission—the first documented instance ever for a mosquito-borne disease. (The couple, along with Kobylinski and others, wrote up their bit of medical history in a 2011 paper in *Emerging Infectious Diseases*, in which they dispassionately refer to themselves as patients 1, 2, and 3.)

Musso and his colleagues also found the virus in the bloody semen of a Zika patient in French Polynesia. Still, the fact that many children and elderly people fell ill suggests that sexual transmission is a "curiosity" rather than playing a major role in Zika's spread, Musso says. The team in Tahiti also documented a case of mother-to-child transmission during birth, and showed that the virus occurred in the blood of 3% of asymptomatic blood donors, a surprisingly high number that suggests a real risk of Zika transmission during transfusions.

Scientifically speaking, Zika is largely terra incognita. A PubMed search for the virus last week turned up just over 200 papers, compared with more than 2500 for chikungunya and more than 14,500 for dengue. There are no drugs or vaccines, and no animal model except monkeys, which aren't practical for most studies. After his own brush with the virus, Foy applied for a National Institutes of Health grant to study the disease but was rejected. Now that Zika appears to be exploding, he expects a wave of new research, as happened for chikungunya, then a similarly obscure agent, after it caused a massive epidemic in Indian Ocean islands in 2005.

For the moment, there is little hope of stopping Zika, Gubler says. Controlling the mosquitoes that carry it is a frustrating affair; *Aedes* breed in ubiquitous small water reservoirs, such as flower pots or abandoned car tires, and spraying insecticides has not been particularly effective.

There is hope, however, that new technologies may eventually help control mosquito populations. For instance, Oxitec, a startup in the United Kingdom that was recently bought by the U.S. synthetic biology company Intrexon, has developed genetically modified sterile male mosquitoes that can bring down a population. Other researchers have infected mosquitoes with the *Wolbachia* bacterium, which reduces their capacity to host pathogens. And long-running attempts to make mosquitoes resistant to pathogens through genetic modification have received a fresh boost from new gene-editing systems (see story, p. 1014). If one or more of these technologies works out and becomes widely adopted, Gubler says, "we could finally see some real progress." ■

BIOMEDICAL RESEARCH

An end to U.S. chimp research

NIH announces plans to retire its last chimpanzees

By **Jocelyn Kaiser**

The U.S. National Institutes of Health (NIH) is ending its support for invasive research on chimpanzees. Agency head Francis Collins said last week that a colony of 50 chimps it had planned to keep in reserve for research—after retiring the rest—is no longer needed. NIH also made clear that it will no longer fund invasive studies on any other chimps. "I think it is the natural next step in what has been a process over the last 5 years, really, of deep thinking about the appropriateness of research on our closest relatives, the chimpanzees," Collins told *Science*.

It's "amazing and historic news," says Kathleen Conlee, vice president of animal research issues for The Humane Society of the United States in Washington, D.C. But some biomedical researchers expressed disappointment. Chimpanzees "have been a critical model for life-saving research" in infectious disease and other areas, and the colony would have been available "in the event there was a national, critical need for research in the future," said a spokesperson for the Texas Biomedical Research Institute in San Antonio, which hosts the Southwest National Primate Research Center.

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> **Francis Collins**, NIH director

NIH announced the move on 18 November, but the news broke earlier when someone at NIH leaked an internal staff email from Collins. In the 16 November memo, he wrote that several factors, including the fact that no researchers have asked to use chimpanzees in recent years, led him to conclude that the 50 animals are no longer needed. "Given this complete absence of interest in a space now approaching 3 years, I think it's fair to say the scientific community has come up with other ways to answer the kinds of questions they used to ask with chimpanzees," Collins says.

The United States, unlike many other countries, has kept the door open for invasive research on chimpanzees but has tightened restrictions. In June 2013, NIH announced it would phase out most agency-funded chimpanzee research and retire all but 50 of its research chimps. As NIH-funded chimpanzee grants ended, investigators would need to meet new and tougher standards to qualify for new grants.

A decision this past June by the U.S. Fish and Wildlife Service (FWS) to list captive chimpanzees as endangered added another hurdle by requiring a permit to use any of the 700 research chimpanzees in the country in invasive research. Researchers wanting to study chimps would also have to show that the work would somehow benefit chimpanzees in the wild.

As a 14 September deadline approached for the FWS requirement, the agency had not received a single research permit application (*Science*, 21 August, p. 777). And NIH has only received one research application—a proposal from an intramural researcher that was later withdrawn, Collins says.

In the leaked email to James Anderson, director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives, Collins describes other factors behind his decision. These included the fact that in 2013, Congress lifted a cap on how much NIH can spend on supporting chimpanzee retirement, and that there is room for more animals at Chimp Haven in Keithville, Louisiana, the federal sanctuary for retired NIH chimps.

Collins has asked Anderson's office to prepare a retirement plan for the 20 or so chimps NIH still owns at the Southwest center and the 140 at MD Anderson Cancer Center's primate facility in Bastrop, Texas. About 150 more chimps at the Alamogordo Primate Facility in New Mexico will be moved later. "We still have work to do," Collins says. But it will be easier, he says, "without having to go through the complicated calculus of which chimps ought to be in the group of 50 to be saved for research."

Collins also asked Anderson to plan to phase out funding for about 82 research chimpanzees at the Southwest center that NIH supports but does not own. And, an NIH spokesperson wrote in an email, "NIH will not fund biomedical (i.e., invasive) research involving chimpanzees (full stop)." ■