



Not so benign. A chikungunya infection can be extremely painful and even fatal.

INFECTIOUS DISEASES

Chikungunya: No Longer a Third World Disease

An explosive outbreak in a remote corner of France—and fears that it may threaten Europe and the United States—have brought fresh attention to an exotic virus

SAINT-PIERRE, LA RÉUNION—To say that few scientists used to care about the chikungunya virus is putting it mildly. The mosquito-borne disease has caused massive outbreaks for at least half a century, but they all happened in developing countries in Asia and Africa. And although the virus causes severe rashes and joint pains, it never seemed to be fatal; many even called it “benign.” Few researchers took an interest.

No longer. Things have changed in large part, researchers say, because chikungunya has finally struck a rich country. In 2005 and 2006, the virus caused a massive outbreak on La Réunion, an island twice the size of New York City 700 kilometers east of Madagascar—and a French *département*. Almost 40% of the population of 785,000 fell ill. In response, the French government mounted a broad research program. A recent meeting* here showed that scientists have learned as much about chikungunya in the past 2 years as in the previous 2 decades.

They have learned that the virus can kill, for instance, that it can be transmitted from mother to child around childbirth, and that a

single-point mutation may have caused it to explode here. They set up the largest screening effort ever to look for animal hosts. And already a once-abandoned vaccine is being prepared for new clinical trials, and new drugs are under study.

To date, French researchers and institutes have published the majority of many dozens of new chikungunya papers, as several speakers proudly noted. (One non-French researcher said he smelled a whiff of scientific chauvinism

in the air.) But other countries are paying close attention as well, as they, too, may be at risk. The big surprise of the outbreak at La Réunion was that the infamous Asian tiger mosquito, which is spreading fast across Europe and the United States, proved an excellent vector. This summer, Italy had a small chikungunya outbreak, the first ever in Europe. There's no reason why the same couldn't happen elsewhere in Europe or in the United States, says Ann Powers, a chikungunya expert at the U.S. Centers for Disease Control and Prevention (CDC) in Fort Collins, Colorado.

Surprise attack

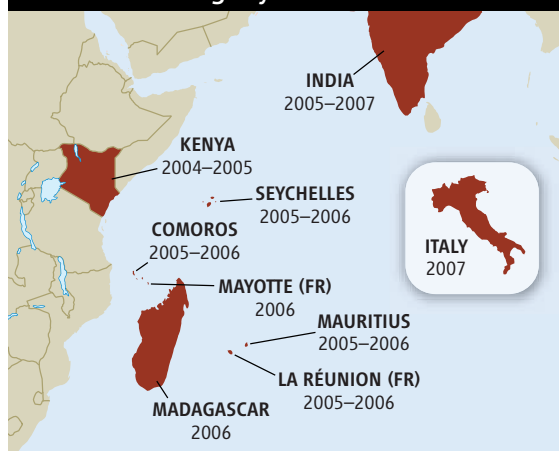
Chikungunya—or “chik,” as some scientists call it—belongs to the alphaviruses, a group that includes the Ross River virus in Australia and the viruses that cause eastern and western equine encephalitis, two serious diseases occurring in the United States. First isolated from a patient in Tanzania in 1953, the chik virus has surfaced occasionally since in countries across Africa, South Asia, and Southeast Asia. It causes high fevers, rash—sometimes with massive blisters—and excruciatingly painful swelling of the joints in fingers, wrists, and ankles.

The outbreak that hit La Réunion appears to have started in Kenya in 2004. It wasn't reported at the time, but in a paper published in 2007, researchers noted that the epidemic started in the coastal towns of Lamu and Mombasa, Kenya. Later, the virus appears to have gone on an island-hopping tour of the Indian Ocean, landing in Madagascar, the Comoro Islands, Mayotte—a much smaller French territory west of Madagascar—Mauritius, and the Seychelles (see map). It reached India, where it hadn't been seen for 32 years, in December 2005, infecting an estimated 1.4 million people so far, Brij Kishore Tyagi of the Centre for Research in Medical Entomology in Madurai reported at the meeting.

La Réunion inhabitants have complained bitterly that mainland France initially appeared to take little interest. Chikungunya first caused a small wave of a few thousand cases between March and July 2005. Then it all but disappeared, only to come roaring back in December. By late January 2006, 47,000 new cases were reported in a single week. Only then was a chikungunya task force set up, led by epidemiologist Antoine Flahault, dean of the French School of Public Health in Rennes and Paris.

La Réunion's location—the flight from Paris takes 11 hours—

Recent Chikungunya Outbreaks



* Chikungunya et Autres Arboviroses Emergentes en Milieu Tropical, 3–4 December.

may have contributed to the response lag, says sociologist Michel Setbon of the National Centre for Scientific Research in Aix-en-Provence, but so did the notion that chikungunya isn't such a big deal. However, the outbreak showed that, although the disease burden may get lost in poor countries facing many other scourges, chikungunya is nastier than people assumed. For starters, some patients—mostly older people with other medical conditions—ended up with severe symptoms, such as respiratory failure or brain infections, and more than 250 of them, about 0.1% of all cases, died. But even for those with milder forms of the disease, the word “benign” seemed hardly appropriate. The joint pains are crippling and can last for months, even years. The outbreak also strained the island's health care system and created economic havoc. The collapse of tourism alone—the main source of income here—caused an estimated \$160 million in losses.

Currently, doctors can do little more than prescribe painkillers and general anti-inflammatory drugs to chikungunya patients, which is why France made drug discovery a priority. Hoping for a quick lead, a team led by virologist Xavier de Lamballerie of the Hôpital de la Timone in Marseille has screened 150 existing drugs—which could gain approval much faster—for activity against chikungunya in cell cultures. When chloroquine, an old antimalarial drug, seemed promising, a clinical trial was set up to test its effects in La Réunion patients. The study got going when the epidemic was on the wane, however, and only 75 patients were enrolled. Among them, the drug showed no benefit.

A subsequent study using a newly developed animal model suggested that the drug may actually do more harm than good. When Roger le Grand and his colleagues at France's Atomic Energy Commission lab in Fontenay-aux-Roses treated infected macaques with chloroquine, it prolonged infection, for reasons that aren't clear yet. That took chloroquine off the table for good, but in the meantime, two other compounds have been found—one already on the market for another disease, and one very close. They inhibit the virus much more potently, says de Lamballerie, who declined to name them.

Meanwhile, a consortium of French institutes is hoping to start safety trials in 2008 with an old vaccine that the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland, developed in the 1980s but later shelved as priorities shifted. The vaccine is derived from a live, weakened chikungunya strain, and USAMRIID has enough of it in its freezers to produce tens of millions of doses, Flahault

says. France has procured two batches, which are now undergoing further testing in the lab; tests in macaques are the next step.

One key question is whether regulatory authorities will allow the use of a vaccine produced decades ago and deep-frozen ever since. If they don't, a pharmaceutical company would need to produce the vaccine from scratch using USAMRIID's old seed virus, which would delay development.

A better vehicle

In Africa, chikungunya is known to be transmitted in a “sylvatic cycle”: The virus lurks in primates when it's not infecting humans. In Asia, such animal hosts have never been discovered; there, chikungunya is assumed to be a humans-only disease. In an attempt to find out whether animals might have played a role in the outbreak in La Réunion, a group led by Michel Brémont of the National Institute for Agricultural

that altered a single amino acid in its envelope protein. Papers published last month by Anna-Bella Failloux of the Pasteur Institute in Paris and her colleagues and a team led by Stephen Higgs of the University of Texas Medical Branch in Galveston have shown that the change makes it much easier for the virus to reproduce in the mosquito's midgut. This leads to 100-fold higher virus concentrations in its salivary glands, which in turn increases the virus's chances of being transmitted during the next bite. Those findings strongly suggest that the mutation helped the virus adapt to the mosquito and “enhanced the epidemic,” says CDC's Powers.

That's worrisome, because *Ae. albopictus*, originally from eastern Asia, has been spreading across the globe during the past 2 decades. The outbreak this summer in Italy—where *Ae. albopictus* is rampant—got started when a chikungunya patient from India traveled to a

small village in the province of Ravenna. Such “imported” cases happen all the time: Mainland France had almost 800 in 2005 and 2006, and the United States 38. It's a matter of time before a patient kicks off a new outbreak in an unexpected place, Higgs says.

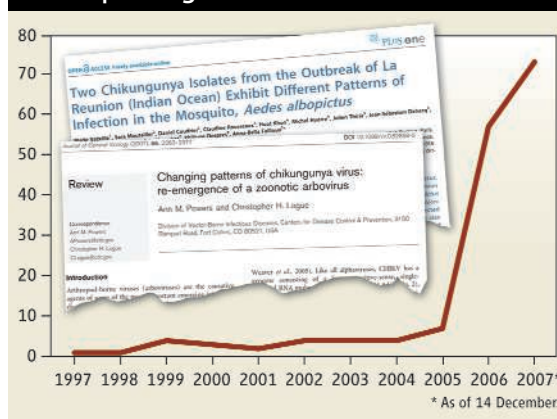
If that happens, controlling mosquitoes is the only way to halt the spread of the virus, but *Ae. albopictus* is notoriously difficult to fight. At La Réunion, government agencies sprayed massive amounts of insecticides; the outbreak ended, but opinions differ on how much spraying contributed. The epidemic may just have run its course.

The Italian government is planning to fight *Ae. albopictus* by releasing massive numbers of sterile males, a technique that has been successfully used to drive down populations of agricultural pests (*Science*, 20 July, p. 312). France is interested in the approach as well, says entomologist Didier Fontenille of the Institute of Research for Development in Montpellier, but it would likely start with *Anopheles arabiensis*, a species that can transmit malaria. Several new, less environmentally disruptive insecticides are under study as well.

Chikungunya has disappeared from La Réunion, and with 38% of the population now immune, it may not return for a long time. Scientists say the outbreak was a unique chance to focus attention—and money—on a tropical pathogen that, unfortunately, may well have a bright future in temperate regions.

—MARTIN ENSERINK

An Exploding Field



Paper trail. The number of papers with “chikungunya” in the title has risen from fewer than five per year before 2004 to more than 70 in 2007.

Research tested almost 4000 animals for signs of infection—from cats, dogs, cows, goats, and sheep to wild birds, rodents, and bats. The tests are still ongoing, but so far, all but a few have come back negative, and there's no indication that any species helped fuel the epidemic.

A more alarming finding is that the Asian tiger mosquito (*Aedes albopictus*) proved to be an efficient vector. Previously, a species called *Ae. aegypti*, which feeds on humans almost exclusively, was always the virus's main vector. *Ae. albopictus*, the predominant species on La Réunion, was considered a poor one, in part because it bites a wide variety of species. But recent studies have suggested why *Ae. albopictus* suddenly became a much better vehicle.

Between the first, small outbreak in early 2005 and the big one that started in December, the virus underwent a point-mutation change