Chikungunya Outbreaks — The Globalization of Vectorborne Diseases

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In 2006, an outbreak of chikungunya fever — an arthralgic disease caused by a mosquito-borne alphavirus — swept over a number of islands in the Indian Ocean (the Comoros, Mauritius, the Seychelles, Madagascar, Mayotte, and Reunion). In Reunion, which has a population of 770,000, there were 265,000 clinical cases (an incidence of 34%), and the disease was implicated in 237 deaths (about 1 per 1000 clinical cases); a recent report by Reunion health authorities indicated that the seroprevalence was 35%, with very few asymptomatic cases. The epidemic had started with outbreaks in Kenya in 2004 and the Comoros early in 2005. More recently, it jumped to India, where there have been an estimated 1.3 million cases to date.[1] When all is said and done, the global toll of chikungunya in 2006 could be close to 2 million, and the disease may well continue to spread this year.

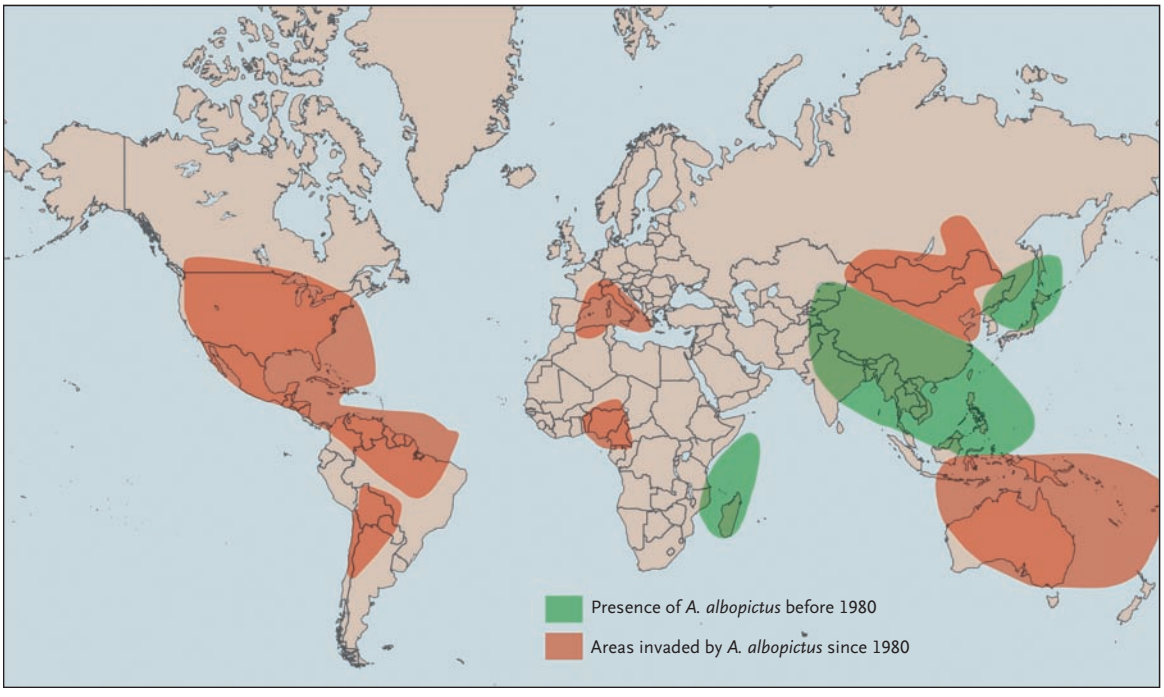
Sequence analysis of the virus genome revealed that this massive outbreak was caused by a new variant.[2] Such changes are common in viruses that have a positive-stranded RNA genome, because the RNA-dependent RNA polymerase has no proofreading activity. A mutation in the E1 envelope gene (*A226V*) has received special attention, and some researchers have proposed that this mutation may have modified the virus's ability to infect mosquitoes or perhaps even the severity of the illness associated with human infection. The mutation was reported to have occurred sometime between the spring and the fall of 2005 — thus it cannot be implicated in the early stages of the epidemic (the Kenyan and Comorian outbreaks) but may be to blame for the adaptation to a new mosquito vector.

In the Makonde language, "chikungunya" means "that which bends up," and joint pains are a major feature of both the acute and the chronic phases of the disease. The ankles and wrists are most commonly involved; intense pain caused by pressure on the wrist is a strong diagnostic sign of the disease.[2] Within 2 to 5 days of infection, conjunctivitis and a rash are common; arthralgias can persist for weeks to months. Previously undescribed severe clinical forms were reported in Reunion, including cases caused by peripartum mother-to-infant transmission and cases involving meningoencephalitis (sometimes in newborns) and hepatic failure (although the liver damage may have resulted from high doses of acetaminophen). Common hematologic abnormalities in the acute phase include lymphopenia and thrombocytopenia that may be associated with bleeding. Levels of hepatic enzymes are commonly increased, and viral loads are remarkably high — frequently above 10^9 virus particles per milliliter of serum.

Aedes albopictus.

Chikungunya was diagnosed in an unprecedentedly large number of people (more than 1000) who were returning to Europe and the United States from the areas where the outbreaks occurred. Such infected people can disseminate the virus and initiate or fuel new epidemics in countries where replication-competent vectors reside, since no antiviral treatment is yet available. Also, as a direct consequence of the high viremia in patients, direct human-to-human transmission can occur, as was demonstrated in southern France.[2]

In Kenya and the Comoros, the vector of the chikungunya virus was *Aedes aegypti*, the vector previously reported to be involved in transmission in Africa and Asia. In contrast, in Reunion and Mauritius, *A. albopictus*, the Asian tiger mosquito, was the primary vector. The devastating outbreak resulted from a human–mosquito–human cycle that, as in dengue, did not require an external nonhuman reservoir. *A. albopictus* is also prevalent in Mayotte and Madagascar,



World Distribution of the *Aedes albopictus* Mosquito.

but it is unclear which vector was involved in most islands of the Comorian archipelago, where studies have not been conducted or are ongoing. There is recent evidence that the outbreak in India, where *A. aegypti* is the primary species of mosquito, was caused by the new variant of the virus.[3] *A. albopictus* is generally considered to have a lower vector capacity for arboviruses than *A. aegypti*. Specific mosquito populations, however, may have a high vector capacity,[4] as suggested by a massive outbreak of dengue that was propagated by *A. albopictus* in Reunion in 1977. It is also possible that the strain of chikungunya virus in the Indian Ocean became better adapted to the *A. albopictus* vector.

Introductions of nonnative species of plants, invertebrates, and vertebrates are increasingly being recognized in countries with temperate climates.[5] Among migrating invertebrate species, mosquitoes that are capable of transmitting infectious diseases are of particular interest. The expansion of global air travel and seaborne trade removes geographic barriers to insect disease vectors, enabling the insects to move great distances in short periods. If they can adapt to the local environment, they establish themselves in new areas. It is thus that mosquitoes of the aedes (stegomyia) genus have gained an increasingly global distribution. In the past 50 years, the anthropophilic *A. albopictus* has spread to all continents (see map) and adapted to most climates. Although long considered a secondary disease vector, it has been shown to be capable of transmitting arboviruses under both laboratory and field conditions.

Like epidemics of dengue and West Nile virus, the chikungunya outbreak is an example of the abrupt expression of vectorborne diseases in the global village. It involved an African virus and an Asian mosquito and started in the Indian Ocean. The establishment of new vectors makes possible the introduction of new pathogens. Malaria, yellow fever, African tickborne rickettsiosis, and more recently, West Nile virus have all been imported from Africa to the Americas. After all, the spread of such vectorborne diseases requires only a host reservoir and a specific vector. If humans are the host reservoir and the vector is widely distributed, globalization of the disease is just a matter of time.

The emergence in 1999 of West Nile virus in the United States and its subsequent rapid spread throughout the country demonstrated that arboviruses can present a threat in developed countries with temperate climates in the absence of herd immunity. One can therefore justifiably spec-

ulate that the chikungunya virus could establish itself in any tropical or temperate area where *A. albopictus* is present today — or where it migrates as its distribution continues to grow. Thus, the key measures for preventing chikungunya epidemics include entomologic surveillance, peridomestic mosquito control, public education, detection of imported cases, and the early recognition of local transmission followed by efficient vector control.

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Dr. Raoult reports that he is a cofounder of INODIAG, a serologic diagnostics company.

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FOCUS ON RESEARCH

DNA Repair and Survival in Lung Cancer — The Two Faces of Janus

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Lung cancer, the most common cause of cancer deaths globally, results in about 1 million deaths each year. Despite advances in treatment over the past two decades, the improvement in long-term survival has been limited: only about 15% of patients survive for 5 years or longer. The high mortality is due mainly to early and widespread dissemination of the cancer, which means that surgical removal of early-stage non–small-cell lung cancer results in the best chance for long-term survival. Chemotherapy for advanced non–small-cell lung cancer (which accounts for about 85% of all lung cancers) or as adjuvant treatment for patients with resected tumors offers modest benefits in improved quality of life and increased survival times.

Currently, the usual chemotherapy regimen combines a platinum-containing drug with another cytotoxic agent. However, platinum-based therapies have drawbacks: severe toxic effects for the patient and drug resistance in the tumor cell. Markers that predict which patients with resected early-stage cancers will survive longest without additional therapy and markers that predict resistance to conventional chemotherapy would be of considerable clinical benefit. The article by Zheng and colleagues in this issue of the *Journal* (pages 800–808) suggests that these two crucial but very different needs may both be filled by a single pair of markers.

Platinum compounds exert their cytotoxic effects by binding covalently to genomic DNA, forming adducts that result in altered forms of DNA. Such couplings activate DNA-repair processes, and unless these adducts are repaired before the DNA replicates, they may lead to nucleotide substitutions, deletions, and chromosome rearrangements (mutagenesis) or to activation of cell-signaling pathways that result in cell death (apoptosis). The three widely used platinum compounds — cisplatin, carboplatin, and oxaliplatin — damage tumors through apoptosis mediated by the activation of the death receptor and mitochondrial pathways.

A number of endogenous and environmental agents cause genomic damage that, unless corrected, lead to cell death or mutations. In turn, these results contribute to aging and carcinogenesis. There are multiple cellular mechanisms for correcting or repairing incorrect, damaged, or broken DNA sequences, but in mammalian cells, nucleotide excision repair is the major pathway for removing damaged bases, including bulky, helix-distorting adducts, from DNA. Much of our knowledge of the nucleotide excision repair process (see diagram) comes from studies of xeroderma pigmentosum, in which inherited mutations of certain crucial nu-