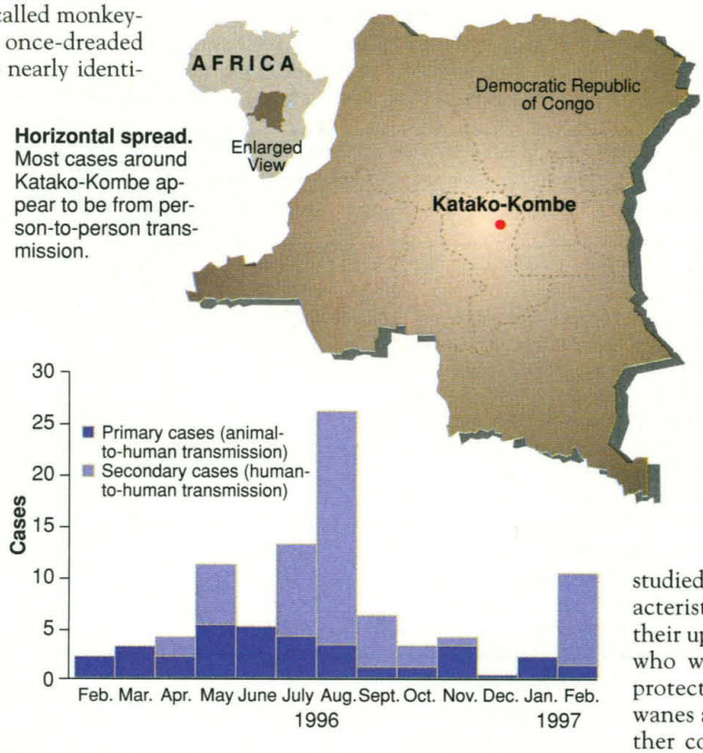
Is an Old Virus Up to New Tricks?

A recent upsurge of monkeypox cases in the Democratic Republic of Congo, in which the virus seems to have jumped from person to person more readily than before, has researchers on full alert

Exotic viruses like hanta, Ebola, and Marburg have become media stars in the past few years, the focus of blow-by-blow news accounts, best-selling books, and doomsday Hollywood thrillers that chart attempts by scientists to thwart the onslaught of these "emerging" pathogens. Yet little has been heard outside the scientific literature and Internet chat groups about an exotic infection that is alarming some public health experts: the largest outbreak ever seen in humans of a well-known virus called monkeypox. A first cousin of the once-dreaded smallpox, monkeypox causes nearly identical symptoms. "I hate to be accused of pushing the alarmist button, but for practical purposes, smallpox is back," says virologist Peter Jahrling of the U.S. Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland.

Although researchers have long known that monkeypox routinely jumps from animals to humans, studies have shown that infections quickly die out, because the virus does not easily pass from one person to another. Yet between February 1996 and February 1997, the Democratic Republic of Congo (formerly Zaire) had at least 92 cases of the disease and three deaths in a remote region where only 37 documented cases were reported from 1981 to 1986. These findings have led to intensive discussions about what might be causing the outbreak—in particular, whether the virus is traveling from human to human more readily than before. The outbreak also has stoked the debate about the pros and cons of retaining samples of the smallpox virus—which has no animal hosts and only exists in two lab freezers—for comparative research with related viruses like monkeypox (see sidebar).

Medical epidemiologist Ali Khan of the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta became seriously worried about the outbreak spreading after visiting the area in February. Khan headed an international team, organized by the World Health Organization (WHO) and the Zairian Ministry of Health, that visited the 12 villages at the center of the outbreak (see map) for 5 days; the trip was cut short because of civil unrest. As Khan and colleagues detailed in the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) on 11 April, they believe 73% of the 89 people they studied were infected by other people. That would be a large jump from the 30% "secondary contact" rate reported by Czechoslovakian epidemiologist Zdeněk Ježek, who did the 1981 to 1986 studies in Zaire and co-authored *the* book on the disease, *Human Monkeypox*. The recent investigation also found one patient who appeared to have been the source of eight other infections, which is twice the highest chain of transmission observed previously. "This is not just an outbreak of some rare, exotic disease in the middle of nowhere," says Khan. "I'm personally concerned about what would happen if this disease showed up in a major city."



Horizontal spread. Most cases around Katako-Kombe appear to be from person-to-person transmission.

SOURCE: CDC

Joel Breman, who formerly headed a monkeypox effort as part of the WHO's smallpox eradication program, says he is "alarmed" by the number of cases in such a small area, the secondary attack rates, and the data on chain of transmission. But Breman, who is now with the Fogarty International Center at the U.S. National Institutes of Health, isn't convinced that human-to-human transmission is increasing. "They really were not there long enough to do a detailed ascertainment of what's going on," says Breman. "I would not want to jump to any conclusions that this is new and radically different from what was going on before." Ježek, a retired consultant with WHO, agrees: "I've seen human-to-human transmission, and it's very difficult to distinguish whether it's an introduction from an animal source."

Success breeds vulnerability

One explanation for the outbreak, floated by Ježek and others, raises a bitter irony: Smallpox vaccinations—which also confer immunity to monkeypox—were so successful that they were stopped nearly 2 decades ago, creating an ever-growing pool of people who are susceptible to the animal virus. Indeed, only 18% of the people studied in the recent outbreak had the characteristic smallpox vaccination scar on their upper left arms. Moreover, even those who were vaccinated may no longer be protected, because, says Ježek, immunity wanes after 5 to 10 years. Immunity is further compromised by this country's high rates of infection with HIV, which cripples immune systems.

The civil war may have contributed another factor: Faced with a growing threat of starvation because of the unrest, villagers may have increased their hunting of animals that carry monkeypox, which include monkeys, squirrels, and rats. "If the population has no sources for food, they start to hunt what is very close," says Ježek. "On the palm trees surrounding the villages, there are plenty of squirrels." Khan and colleagues attempted to investigate this possibility during their recent trip, collecting blood samples from 64 squirrels (one of which had a suspect lesion), rats, and other animals. These samples still are being analyzed.

Smallpox: Clues From a Killer

Nearly 4 years ago, *Science* ran side-by-side Policy Forums, written by groups of prominent researchers, arguing for and against destroying the world's only remaining stocks of smallpox virus (*Science*, 19 November 1993, pp. 1223 and 1225). A main argument made by the proponents of keeping the two stocks—which reside only at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta and at the Research Institute for Viral Preparations in Moscow—was that studies of smallpox might help combat another member of the *Orthopoxvirus* family, monkeypox. Now the monkeypox outbreak in the Democratic Republic of Congo (see main text)—which has yielded more cases than ever before, and more human-to-human transmissions—has strengthened the convictions of those researchers. "The fact that monkeypox outbreaks are still occurring, and are not going to be eliminated, is a strong argument for retaining [the stocks]," says Duke University's Wolfgang Joklik, first author of that editorial.

Sergei Shchelkunov of the State Research Center of Virology and Biotechnology in Koltsovo, Russia, is now sequencing the complete genome of monkeypox. Once that is completed, he argues that researchers will need live smallpox virus (which already has been sequenced) to test their new ideas about how the poxviruses cause disease. "I believe we will carry out some laboratory experiments in the future with smallpox virus," contends Shchelkunov, who is collaborating with a co-author of the save-smallpox editorial, Bernard Moss of the National Institute of Allergy and Infectious Diseases. "Without this virus, it will be impossible to get that extremely important information." For example, several researchers say the only way to tease out why monkeypox is less infectious to humans than smallpox—to determine if the viruses use different receptors to enter cells, for example—is with live viruses.

Yet virologist Joseph J. Esposito of the CDC, another collaborator on the monkeypox sequencing project, doesn't think the remaining smallpox is needed to combat monkeypox. "I don't think monkeypox is going to fill a niche that smallpox left behind," says Esposito. "We're pretty far advanced, and we can bring these viruses under control."

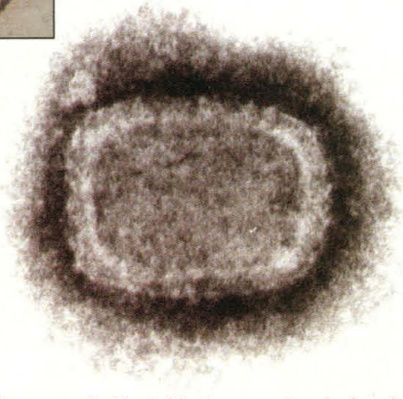
Zdeněk Ježek, co-author of the main book on monkeypox and a former World Health Organization consultant, sees eradicating the smallpox virus simply as a necessary last step that must be taken, and this outbreak changes nothing. "Keeping smallpox is something like a stamp collection," says Ježek. "People are afraid it will disappear from their collections." Plans call for destroying the remaining isolates on 30 June 1999, although a World Health Assembly meeting the month before could stay the execution. **–J.C.**

A more frightening hypothesis is that monkeypox really has changed, becoming more virulent or more transmissible. But, as reported in the *MMWR* article, researchers have genetically analyzed part of one isolate from a person infected in 1996, and there's no evidence that it differs from strains collected in Zaire between 1970 and 1979. In a 17 May letter in *The Lancet*, Khan and several of his international colleagues emphasize this point, stressing that "notions of monkeypox virus mutating into [smallpox] virus are unfounded." Researchers are, however, concerned that a monkeypox variant could have found its own way to become more adapted to the human host—which would be an ominous prospect. "This could be worse than smallpox if it adapts to humans," acknowledges virologist Bernard Moss of the National Institute of Allergy and Infectious Diseases (NIAID). "Then we'd have smallpox with an animal reservoir. How's that for a scenario?" Fortunately, there is no evidence so far to support such a scenario.

WHO

The Army's Jahrling thinks "the probability is low" that this outbreak will spread further. "But it's not zero," he adds. Because of that possibility, Jahrling convinced the military to give U.S. troops the smallpox vaccine if they should be ordered into this region. But researchers are reluctant to recommend a new vaccination program for the local population, because the vaccine can cause disease and death in people whose immune systems have been decimated by HIV. "The number and the frequency of side effects from the vaccine would be much higher than the cases of monkeypox," predicts Ježek.

That quandary led the CDC's Joseph J. Esposito, who co-authored the *Lancet* paper and since 1973 has studied the *Orthopoxvirus* family—to which monkeypox belongs—to the idea of giving these vulnerable populations a weakened version of the smallpox vaccine, known as MVA. But it's unclear whether MVA, which decades ago was tested extensively in Germany against smallpox, would protect against monkeypox. He would now like to test that hypothesis in monkeys. Esposito says there is also the chance a new drug might help. In collaboration with U.S. Army and NIAID researchers, he has been studying drugs that are already in human trials for other diseases and, in test tube experiments, appear to have antiviral activity against monkeypox, cowpox, and even smallpox (which he determined by tests with three smallpox strains in storage at CDC).



J. J. ESPOSITO/CDC

Cause and effect. Monkeypox virus isolated from skin lesion, and infected child.

For now, health authorities are trying to keep an eye on the outbreak. The United Nations Integrated Regional Information Network put out a bulletin on 20 March warning that the retreating Zairian soldiers—who were responsible for Khan and colleagues fleeing the country—were moving through the very region where the outbreak occurred. The bulletin also noted that aid workers in the region were worried that Rwandan refugees in poor health were heading toward the region and "could contribute to an escalation in the number of cases and its spread."

To get a closer look, WHO hopes to organize another mission in a month if the political situation calms down enough. Khan is anxious to return. "It's important to get back out there and ask 'What's the magnitude of disease?' and 'How does transmission occur?' " says Khan. "We're all waiting for better data."

–Jon Cohen