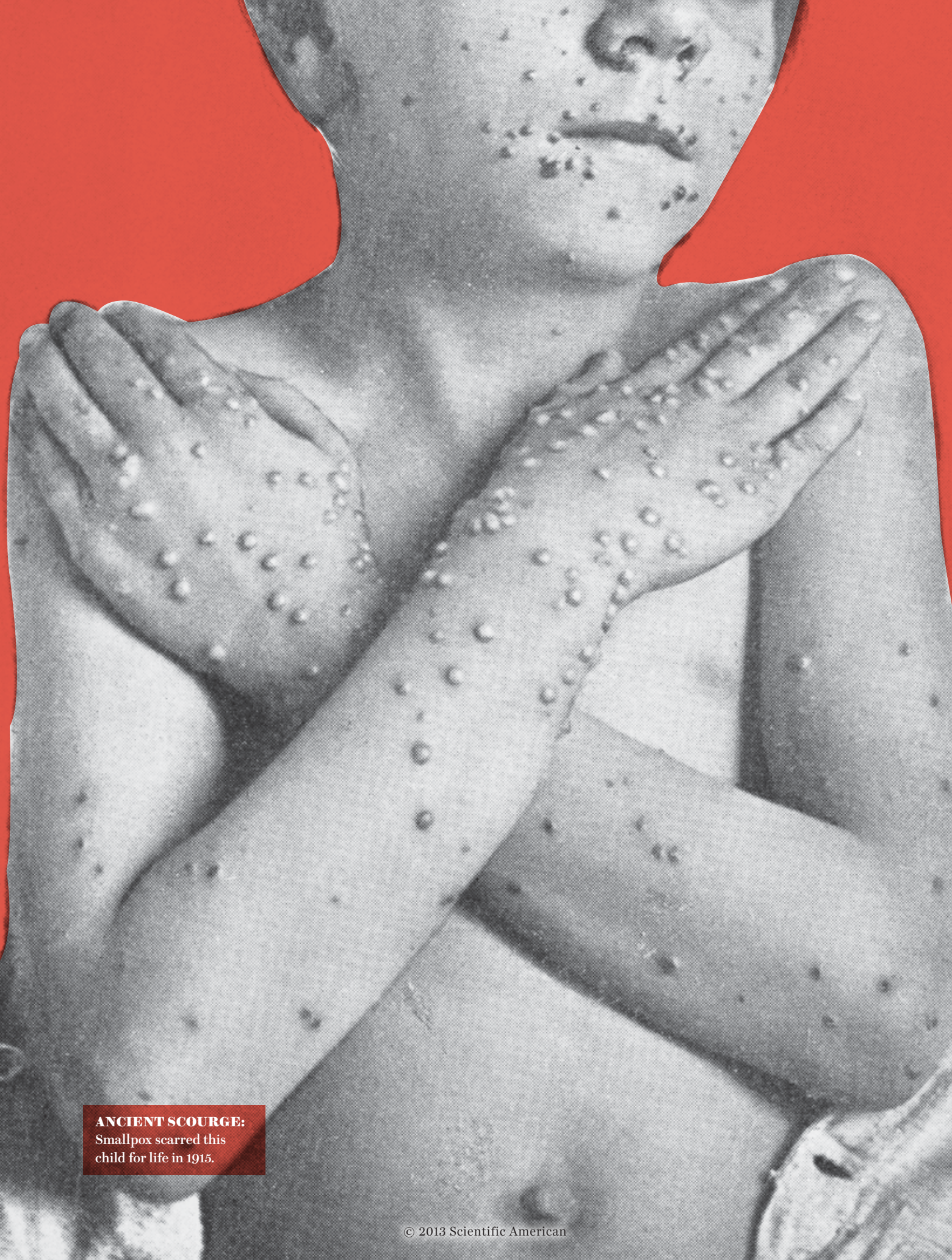


ANCIENT SCOURGE: Smallpox scarred this child for life in 1915.

Sonia Shah is a science journalist and author of *The Fever: How Malaria Has Ruled Humankind for 500,000 Years*. She is currently writing a new book on emerging diseases.

EMERGING DISEASES

NEW THREAT FROM POXVIRUSES

Smallpox may be gone, but its viral cousins—monkeypox and cowpox—are staging a comeback

By Sonia Shah

TEN THOUSAND YEARS AGO, WHEN SMALLPOX FIRST EMERGED, HUMANKIND COULD do little more than pray to the gods for succor. Later known as variola, the virus that caused the disease first attacked the linings of the nose or throat, spreading throughout the body until a characteristic rash followed by virus-filled blisters developed on the skin. Over the course of recorded history, the "speckled monster" killed up to a third of the people it infected. During the 20th century alone, it felled more than 300 million men, women and children.

IN BRIEF

When smallpox was eradicated 35 years ago, people stopped getting vaccinated against it.
In the intervening years the general population has lost immunity not only to smallpox but also to other poxviruses that were formerly held in check by the smallpox vaccine.
The number of cases of monkeypox and cowpox has started to climb, raising the possibility of a new global scourge spreading in smallpox's place.

CORBIS

By the late 1970s, however, the deadly scourge had been eliminated from the face of the earth thanks to mass vaccination campaigns that protected millions and left them with a small scar on their upper arm. With nowhere to hide in the natural world—humans are the virus's only host—variola was beaten into extinction. Today the only known viral samples are locked in two specialized government laboratories, one in the U.S. and the other in Russia. Absent a catastrophic lab accident, deliberate release or the genetic reengineering of the virus, smallpox will never again spread death and misery across the globe.

The World Health Organization, which had organized the eradication campaign, sounded the official all clear in 1979, two years after the last sporadic case was recorded, in a Somali hospital worker. Since then, no country has routinely vaccinated its citizens against smallpox, although the U.S. began inoculating certain health personnel and selected members of its armed forces after the terror attacks on September 11, 2001. Thus, an entire generation has reached adulthood without any exposure to either the disease or the vaccine, which sometimes caused serious side effects.

And therein lies the rub. The smallpox vaccine did not protect just against the variola virus. Anyone who was vaccinated against smallpox also developed immunity to infection with variola's viral cousins—including monkeypox and cowpox. Given the much larger scale of smallpox infections at the time, this secondary protection was seen as a minor benefit.

Now that the smallpox vaccine is no longer widely given, the question becomes: Could these obscure pathogens, which, like smallpox, belong to the *Orthopoxvirus* genus, pose a new danger to humans? There are reasons to worry. Unlike smallpox, cowpox and monkeypox naturally lurk in rodents and other creatures, so they can never be fully eliminated. The number of cases of monkeypox and cowpox in humans has steadily risen in recent years. And both viruses have begun to infect different creatures beyond their normal hosts, raising the possibility that they might spread through new paths around the planet.

No one knows how monkeypox and cowpox will change over time, but virologists worry that if they mutate to jump more easily from one person to the next, they could devastate large parts of the globe. That grim possibility drives a small band of virologists to learn more about these—or any other—potential pox plagues in the making, so as to sound the alarm if they show signs of developing into more threatening forms.

VARYING SEVERITY

THE HISTORY AND BIOLOGY of poxviruses offer some clues as to what to expect from smallpox's kin in the future. Historically, 60 percent of the pathogens that plague humankind, including the orthopoxviruses, have originated in the bodies of other vertebrates. Variola's closest living relative, taterapox, was isolated from a wild gerbil in Africa in 1968. Molecular analyses suggest that smallpox's evolutionary ancestor probably got its start in an African rodent species, possibly now extinct. Similarly, cowpox and monkeypox, despite their names, live in voles, squirrels or other wild rodents.

When variola's ancestor first jumped into humans, it probably was not very contagious, says microbiologist Mark Buller of Saint Louis University. Then, somewhere along the line, he and other researchers surmise, a variant emerged that was much more transmissible. The critical change allowed the virus to broadcast itself via the coughs, exhalations or sneezes of an infected person. Meanwhile human beings started living in much closer quarters, making it that much more likely for one person to pass the infection on to another. The combination of the biological change and the altered environment gave the emerging virus the edge it needed to become a global scourge.

Just because a virus is easily transmitted, however, does not necessarily make it lethal. Indeed, scientists still cannot explain why poxviruses vary so greatly in their severity. In most people, cowpox, camelpox and raccoonpox infections trigger little more than a skin rash, with virus-filled pustules that harmlessly clear up on their own. Monkeypox infections, on the other hand, can be quite deadly in humans. Even at that, not all monkeypox viruses are equally dangerous. The worst subtype, found in the Congo Basin, kills about 10 percent of people who are infected, whereas another version, from West Africa, rarely if ever ends in death. As it happens, the West African strain in 2003 caused the first-ever recorded cases of monkeypox in the Western Hemisphere. The outbreak, which occurred in six states in the U.S., led to the hospitalization of 19 people, including a child who suffered encephalitis and a woman who was blinded, necessitating a corneal transplant. Investigators traced the infection to rodents imported from Ghana that passed the virus to pet prairie dogs, which in turn infected their owners. Such intermediary animals allow a virus that normally lives in animals with little human contact to reach potentially large numbers of people.

Subtle genetic differences may help explain the shifting severity of pox infections. For example, some poxviruses possess genes for proteins that interfere with the ability of the immune system to respond effectively to the infection. When researchers compared the genes from different poxviruses, they zeroed in on one that was found in several different kinds of poxviruses. In the most deadly strains of variola, this gene triggered the production of a protein that evidence suggests prevents some immune cells from efficiently coordinating their counterattack against the virus. But the equivalent gene in the Congo Basin strains of monkeypox (which are less deadly than smallpox) provided the hereditary instructions for a much shorter protein. When researchers looked at the milder West African version of monkeypox, the gene was missing altogether and the protein in question could not be manufactured. Thus, the evidence suggested that the shorter protein in the Congo Basin strains of monkeypox somehow made them less deadly than smallpox.

Speculation among researchers about how different species of poxvirus acquired this and other genes indicates why monkeypox and its cousins could potentially become more dangerous threats than they are now. The genes, which are not essential for poxvirus replication, appear to be faithful copies of genes the viruses acquired at some point in the evolutionary past from organisms they infected. Yet, curiously, the viruses do not in the normal course of an infective cycle come anywhere near the genetic material stored in the nucleus of the host cells.

One possible explanation, popular among pox virologists, posits the simultaneous infection of a human or other vertebrate host with a poxvirus and a retrovirus. Such co-infections are probably pretty common, researchers say. Retroviruses are

known for incorporating their own genes into their host's DNA. (About 8 percent of the human genome consists of DNA that originated in retroviruses.) It is possible that the unusual biochemical activity of the retrovirus inside the cell could allow the poxvirus to capture its host's genes.

If true, this hypothesis could prove portentous. Poxviruses are genetically stable and do not usually mutate quickly. If they can steal genes from their hosts that make them more virulent, then there is no predicting what a relatively harmless, not to mention an already deadly, poxvirus might do under the right circumstances. The change from mild to dangerous threat could occur more quickly and unpredictably than anyone might have previously suspected.

SMALLPOX'S "LITTLE COUSIN"

MONKEYPOX IS BETTER poised than any of its viral cousins at present to emerge as a global threat. Virologists refer to it as smallpox's "little cousin," in part because it causes an illness that is clinically indistinguishable from smallpox. First reported in captive monkeys in 1957, the virus typically lives, evidence suggests, in African rodents, possibly rope squirrels. Outbreaks have so far occurred mostly in Central Africa, with the notable exceptions of the U.S. in 2003 and Sudan in 2006.

University of California, Los Angeles, epidemiologist Anne W. Rimoin was in Kinshasa, Democratic Republic of the Congo, in 2002, when she first heard about local residents who had fallen ill with monkeypox. She did not know how many people were infected, how they were exposed to the virus or whether the virus could spread to others. But she knew the disease was life-threatening and wanted to learn more.

With her blond hair and buff pedicure, Rimoin could hardly be mistaken for a local in the remote Congolese jungles. Yet she had studied the country's politics as an undergraduate in African history and was fluent in French, which is still spoken in the former Belgian colony, as well as Lingala and other local languages. She started asking around. "I just clicked with the right people and asked the right questions," she says. And "it became clear to me that there were probably a lot more cases than were being reported."

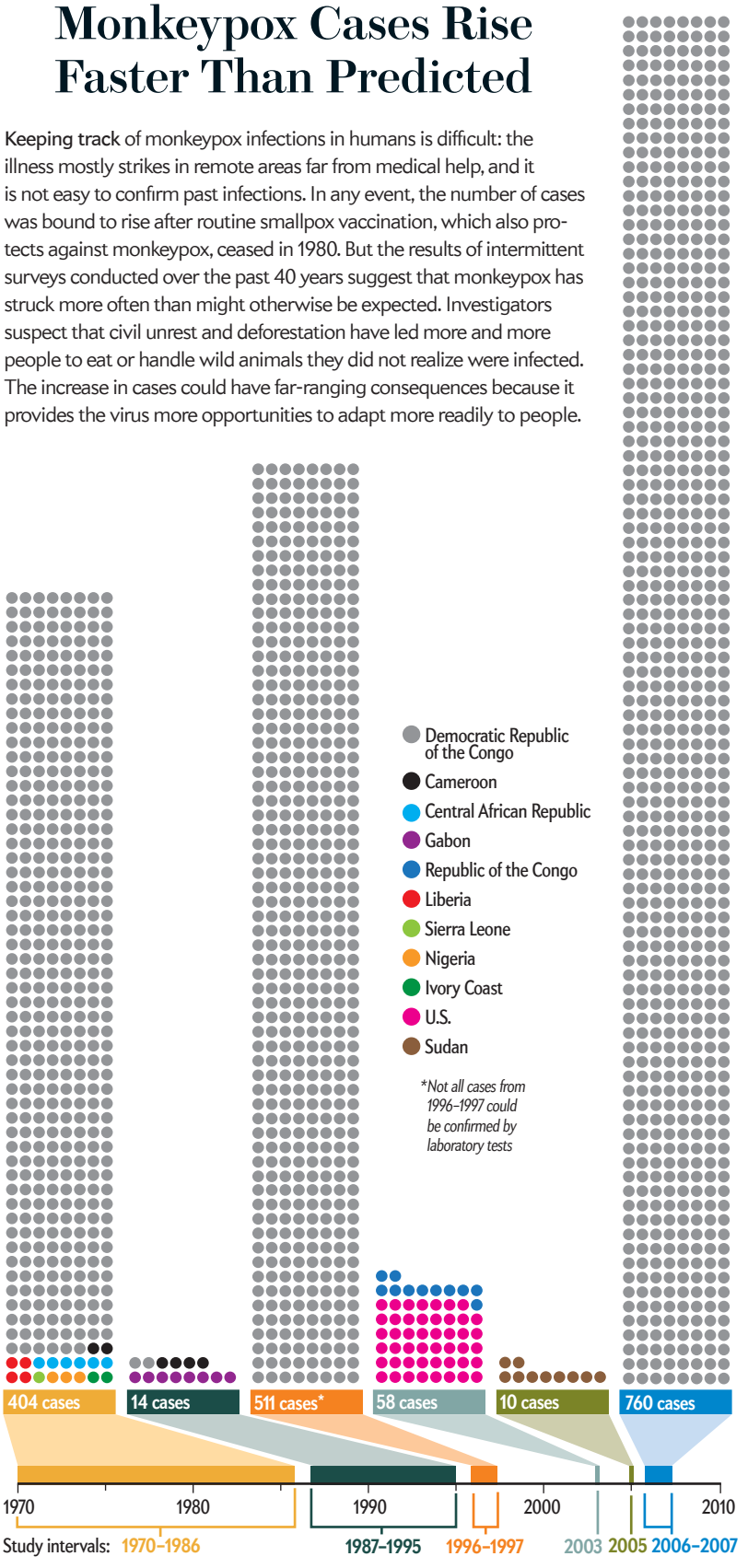
But how to find them? Unsurprisingly, given the dearth of health care facilities in

SOURCES: "MONKEYPOX: AN EMERGING INFECTION FOR HUMANS?" BY JOEL G. BREMAN, IN *EMERGING INFECTIONS 4*, EDITED BY W. M. SCHELD, W. A. CRAIG AND J. M. HUGHES. ASM PRESS, 2000; "OUTBREAKS OF HUMAN MONKEYPOX AFTER CESSATION OF SMALLPOX VACCINATION," BY MARY G. REYNOLDS AND INGER K. DAMON, IN *TRENDS IN MICROBIOLOGY*, VOL. 20, NO. 2; FEBRUARY 2012

WORRISOME TREND

Monkeypox Cases Rise Faster Than Predicted

Keeping track of monkeypox infections in humans is difficult: the illness mostly strikes in remote areas far from medical help, and it is not easy to confirm past infections. In any event, the number of cases was bound to rise after routine smallpox vaccination, which also protects against monkeypox, ceased in 1980. But the results of intermittent surveys conducted over the past 40 years suggest that monkeypox has struck more often than might otherwise be expected. Investigators suspect that civil unrest and deforestation have led more and more people to eat or handle wild animals they did not realize were infected. The increase in cases could have far-ranging consequences because it provides the virus more opportunities to adapt more readily to people.



Graphic by Jen Christiansen

rural Congo, few people who were sick sought out clinicians. And those who had recovered could not easily be identified with blood tests because there was no way of telling whether the presence of antibodies against poxvirus was the result of an earlier smallpox vaccination or another poxvirus infection. Assessing the incidence of monkeypox required finding people who were in the throes of an acute monkeypox infection, when it would be possible to test for the virus itself from the pustules on the skin.

Rimoin began her quest by establishing a research site deep in the forest. There were no roads, no cell-phone signals and no radio transmission. She chartered planes to get in and out and spent days walking and traveling by canoe and by motorcycle to track down monkeypox cases among the Lingala-speaking villagers of interior Congo.

The results were alarming. Compared with similar data collected by the World Health Organization in 1981–1986, Rimoin had found a 20-fold increase in the number of human monkeypox cases. Even so, she believes that her findings, which were published in 2010, are an underestimate. "It's the tip of the iceberg," she asserts. After all, the WHO had a much bigger and much better financed operation looking for monkeypox 30 years ago. Rimoin's team undoubtedly missed many more cases, relatively speaking, than that earlier, larger effort.

RISE OF MONKEYPOX

ALTHOUGH THE SPIKE in monkeypox cases was larger than anyone had anticipated, it was not unexpected. After all, most of the country's population is unvaccinated against poxviruses. (The Democratic Republic of the Congo stopped vaccinating against smallpox in 1980.)

Further research suggested that something else was going on as well. Ecologist James Lloyd-Smith, one of Rimoin's colleagues at U.C.L.A., uses computer models to study how diseases jump from animals to humans. According to his analyses of Rimoin's data, the withdrawal of the smallpox vaccine and subsequent loss of immunity to related poxviruses could not fully account for the spike in cases. There must have also been at least a fivefold increase in "spillover" events, he says, in which the virus jumped from infected rodents into humans.

With expanded opportunities to infect people, monkeypox might better adapt to humans. A few tweaks to a current viral trait may be all that is needed to make it a much more contagious pathogen.

Why monkeypox might be jumping into humans more frequently is a matter of conjecture. It could be that continued clearing of land for agricultural use and for burning wood has put more and more people in contact with infected squirrels, mice and other rodents. In addition, more local people may have been reduced to eating potentially infected animals as a result of the Congolese civil war. A 2009 survey, published in October 2011, found that a third of people in rural Congo eat rodents found dead in the forest and that, suggestively, 35 percent of monkeypox cases occur during hunting and farming season. (Most people contract monkeypox from close contact with infected animals, such as handling or eating them.)

Rimoin and other virologists worry that with expanded opportunities to infect people, monkeypox might better adapt to the human body. Buller studies the ways in which orthopoxviruses cause diseases in both humans and animals. Monkeypox "can already kill people," he says, and it can spread between individuals, too—just not that well. All that may be needed to transform monkeypox into a much more contagious human pathogen might be a few minor tweaks to a current viral trait.

SPREAD OF COWPOX

REPORTS OF PEOPLE and animals infected with rodent-borne cowpox virus are rising as well—in this case, in Europe.

Cowpox infections are mild in most people. After the virus enters cells and disarms the host's initial immune response, a fusillade of virus-hunting antibodies made by the victim prevents the pathogen from spreading to tissues throughout the body. Not so in people whose immune systems have been weakened, such as by HIV, cancer chemotherapy or treatment to prevent the rejection of transplanted organs. "They can get a smallpoxlike disease, and they can die," says Malcolm Bennett of the University of Liverpool in England. Since 1972, public health experts estimate, the number of immunocompromised people in the U.S. who are now susceptible to serious disease from cowpox and other poxviruses has grown 100-fold.

Bennett, a veterinary pathologist, studies the ecology and evolution of cowpox in wildlife. In the U.K., he says, cowpox normally resides harmlessly in bank voles, field voles and wood mice. Domestic cats pick up the virus from the rodents they hunt. They then expose the people who care for them (often at close range) to cowpox, a chain of events that accounts for half of all human cowpox cases in the U.K.

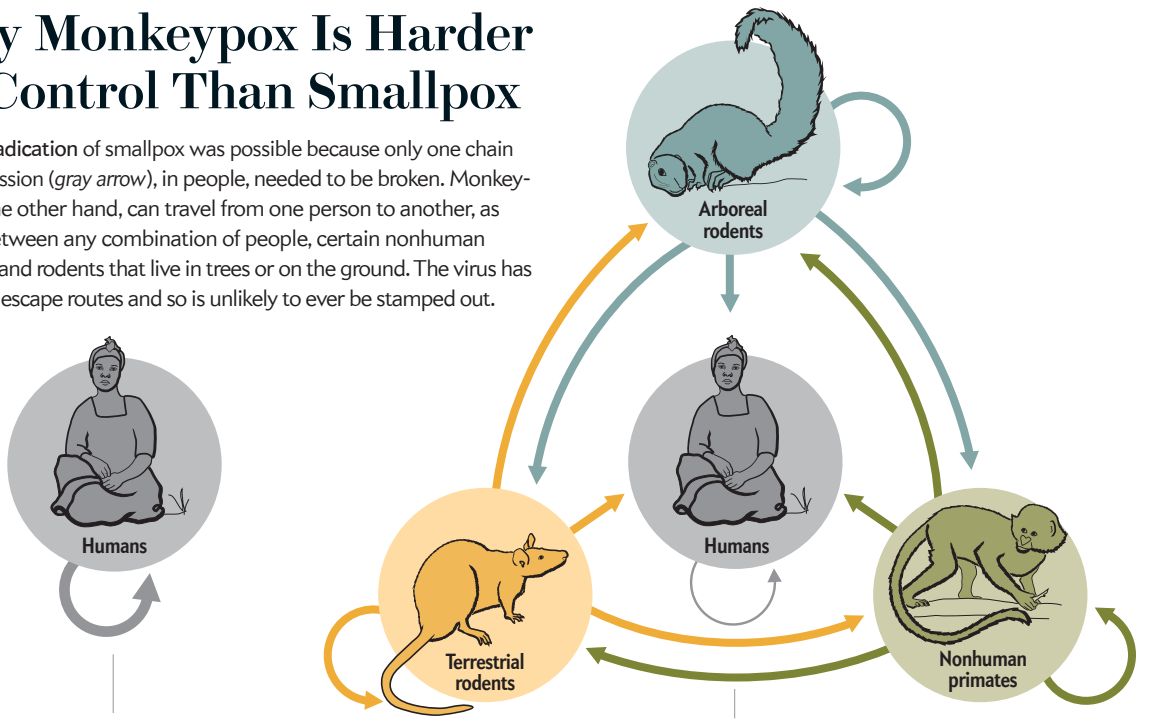
Like monkeypox, cowpox has started making forays into creatures outside its normal reservoir hosts. With bank vole populations booming thanks to mild winters and other favorable climatic conditions, rats may have started playing an intermediary role in cowpox transmission similar to the one played by prairie dogs in the 2003 American outbreak of monkeypox. "There's been a proliferation of reports, either zoo-related or pet-related, associated with rats," says Mary Reynolds, an epidemiologist at the U.S. Centers for Disease Control and Prevention. That trend "is potentially quite concerning because black and brown rats sure make their way around the globe pretty efficiently," she notes. If cowpox becomes established in rats, as opposed to just voles and wood mice, millions more people could be readily infected by, for example, being bitten or coming into contact with their droppings.

Indeed, orthopoxviruses are notoriously adept at colonizing new species. The vaccinia virus, for example, which was used to create modern smallpox vaccines, now freely propagates in dairy cattle in Brazil, as well as in buffalo in India. And there are "a range of orthopoxviruses out there that have never been isolated or fully characterized," Reynolds points out. Given the right opportunities, those less familiar pox strains could extend their ranges into new regions and species. "Some will be pathogenic to people," Bennett adds. "They just haven't managed to make the species jump yet."

MANY PATHWAYS TO INFECTION

Why Monkeypox Is Harder to Control Than Smallpox

Global eradication of smallpox was possible because only one chain of transmission (*gray arrow*), in people, needed to be broken. Monkeypox, on the other hand, can travel from one person to another, as well as between any combination of people, certain nonhuman primates, and rodents that live in trees or on the ground. The virus has too many escape routes and so is unlikely to ever be stamped out.



ARMED AND VIGILANT

AS THE CROWD of people who have never received a smallpox vaccination grows, pox virologists expect the incidence of human cases of monkeypox, cowpox and other poxviruses to continue to rise.

Should any of these poxviruses become adept at plaguing humans, new drugs and vaccines—and the resources necessary to use them—will be needed to contain the threat. Because of post-9/11 fears of intentional releases of smallpox, a spate of new vaccines and drugs are being developed to fight smallpox. These medications will likely provide protection against naturally emerging poxviruses as well. But producing and distributing them, as well as safeguarding against their inevitable side effects, will be a complex and costly undertaking. New smallpox vaccines, such as Bavarian-Nordic's Imvamune, have been designed to be safely administered even to immunocompromised people, but they must be given in higher doses and over the course of two shots instead of one, making them more expensive than traditional smallpox vaccines. A new drug, manufactured by Siga Technologies and known as ST 246, prevents orthopoxviruses from traveling from one cell to another in a host. Despite not yet being approved by the U.S. Food and Drug Administration, the federal government has already purchased a large amount of ST 246 and added it to the national biodefense stockpile.

In places such as the rural Congo River basin, where health financing for cutting-edge new vaccines and drugs is limited, the best hope for now seems to be enhanced surveillance, combined with community education programs. For example, a monkeypox education program run by the CDC, in conjunction with local health officials and voluntary nongovernmental organizations in the Democratic Republic of the Congo, increased the proportion of local people able to recognize monkeypox cases from 23 to 61 percent. Rimoin's arduous surveillance of monkeypox continues as well, with new studies aimed at sequencing the genes in variants infecting animals and people today to see how the virus may be changing. Better detection means more opportunity to care for and isolate infected individuals, squelching chances for the virus to mutate into new forms that spread more efficiently between people.

The ancient war between poxviruses and humans may not have ended when that 21-year-old Somali hospital worker cleared his smallpox infection back in 1977. With new tools and better surveillance, scientists are better armed and more vigilant than ever before. But to prevent another pox from falling on humankind, society will need to maintain those defenses for some time to come. SA

SOURCE: "HUMAN MONKEYPOX: AN EMERGING ZOONOTIC DISEASE," BY SCOTT PARKER, ANTHONY NUARA, R. MARK L. BULLER AND DENISE A. SCHULTZ, IN *FUTURE MICROBIOLOGY*, VOL. 2, NO. 1, 2007

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Anne W. Rimoin's U.C.L.A. laboratory Web site, including photo gallery, publications and press: www.ph.ucla.edu/epi/faculty/rimoin/rimoin.html

SCIENTIFIC AMERICAN ONLINE

Watch as Anne W. Rimoin describes her research into the spread of human monkeypox at ScientificAmerican.com/mar2013/rimoin-video

Illustration by Portia Sloan Rollings