Monkeypox outbreaks: 4 key questions researchers have

Scientists are racing to understand the latest monkeypox outbreaks — from their origins to whether they can be contained.

It's been almost five weeks since public-health authorities confirmed a case of monkeypox in the United Kingdom. Since then, the number of confirmed or suspected cases to emerge in non-African nations has exceeded 1,000. It is the largest outbreak ever seen outside Africa, and has so far affected at least 30 countries, including Canada, Portugal and Spain. The situation has scientists on alert, because the monkeypox virus has emerged in separate populations across multiple countries, and there is no obvious link between many of the clusters, raising the possibility of undetected local transmission of the virus.

"There is still a lot to be learned," says Anne Rimoin, an epidemiologist at the University of California, Los Angeles, who has studied monkeypox in the Democratic Republic of the Congo for more than a decade.

Nature outlines some of the key questions about the recent outbreaks that researchers are racing to answer.

How did the current outbreaks start?

Since the latest outbreaks began, researchers have sequenced viral genomes collected from people with monkeypox in countries including Belgium, France, Germany, Portugal and the United States. One of the most important insights they have gained is that each of the sequences closely resembles that of a monkeypox strain found in West Africa. The strain has a death rate of less than 1% in poor, rural populations, making it much less lethal than another that has been detected in Central Africa. That one has a fatality rate of up to 10%.

Clues have also emerged about how the outbreak might have begun. Although researchers need more data to confirm their suspicions, the sequences they have evaluated are nearly identical, suggesting that a thorough epidemiological investigation might find that the recent outbreaks outside Africa all link back to a single case.

The current sequences are most similar to those from a smattering of monkeypox cases that arose outside Africa in 2018 and 2019 that were linked to travel in West Africa. The simplest explanation is that the person who had the first non-African case this year — who has still not been identified — became infected through contact with an animal or human carrying the virus while visiting a similar part of Africa, says Bernie Moss, a virologist at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

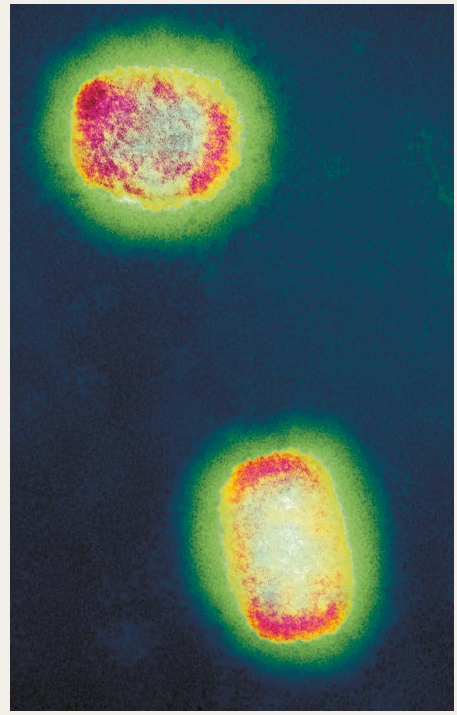
But other explanations cannot be ruled out, says Gustavo Palacios, a virologist at the Icahn School of Medicine at Mount Sinai in New York City. It's possible that the virus was already circulating, undetected, outside Africa in humans or animals, having been introduced during earlier outbreaks. However, this hypothesis is less likely, because monkeypox usually causes visible lesions on people's bodies — which would probably be brought to the attention of a physician.

Could a genetic change in the virus explain the latest outbreaks?

Understanding whether there is a genetic basis for the virus's unprecedented spread outside Africa will be incredibly difficult, says Elliot Lefkowitz, a computational virologist at the University of Alabama at Birmingham who has studied poxvirus evolution. Researchers are still struggling to determine precisely which genes are responsible for the higher virulence and transmissibility of the Central African strain compared with the West African one — more than 17 years after they identified a difference between the two.

One reason for this is that poxvirus genomes contain many mysteries, Lefkowitz says. The monkeypox genome is huge relative to that of many other viruses — it is more than six times as large as the genome for the SARS-CoV-2 coronavirus. That means monkeypox genomes are at least "six times harder to analyse", says Rachel Roper, a virologist at East Carolina University in Greenville, North Carolina.

Another reason, Palacios says, is that few resources have been dedicated to genomic-surveillance efforts in Africa, where monkeypox has been a public-health concern for many years. So virologists are in the dark, because they have few sequences to which they can compare the new monkeypox sequences, he says. Funding agencies have not heeded scientists, who have been warning for more than a decade that further monkeypox outbreaks could occur, he adds.



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Monkeypox virus is a double-stranded DNA virus that replicates inside cells' cytoplasm.

Ifedayo Adetifa, the head of the Nigeria Centre for Disease Control in Abuja, says that African virologists he's spoken to have expressed irritation that they've struggled to garner funding and publish studies about monkeypox for years — but that now it has spread outside the continent, public-health authorities worldwide suddenly seem interested.

To understand how the virus evolves, it would also be useful to sequence the virus in animals, Palacios says. The virus is known to infect animals — mainly rodents such as squirrels and rats — but scientists have yet to discover its natural animal reservoir in the affected areas of Africa.

Can the outbreaks be contained?

Since the current outbreaks began, some nations have been procuring smallpox vaccines, which are thought to be highly effective against monkeypox, because the viruses are related. Unlike some vaccines against COVID-19, which take up to two weeks after a second dose to offer full protection, smallpox vaccines are thought to protect against monkeypox infection if given within four days of exposure, because of the virus's long incubation period, according to the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

If deployed, the vaccines would probably be used in a 'ring vaccination' strategy, which would inoculate close contacts of infected people. In late May, Andrea McCollum, an epidemiologist who heads the poxvirus team at the CDC, said that the agency was not yet deploying such a strategy.

Even if public-health officials can halt the transmission of monkeypox in humans during the current outbreaks, virologists are concerned that the virus could spill back into animals. Having new reservoirs of virus in animals would increase the probability of it being transmitted to people again and again, in countries including those that don't have any known animal reservoirs of the virus. On 23 May, the European Centre for Disease Prevention and Control highlighted this possibility, but deemed the probability "very low".

Is the virus spreading differently compared with previous outbreaks?

Monkeypox virus is known to spread through close contact with the lesions, bodily fluids and respiratory droplets of infected people or animals. Health officials have linked the recent cases to sexual activity, but that doesn't mean that the virus is more contagious or is transmitted sexually, Rimoin says. Unlike SARS-CoV-2, which isn't thought to linger on surfaces much, poxviruses can survive for a long time outside the body, making surfaces such as bedsheets and doorknobs potential vectors of transmission, Roper says.

Although officials have noted that many cases have been among men who have sex with men (MSM), Rimoin emphasizes that the most likely explanation for the virus's spread among MSM groups is that the virus was coincidentally introduced into the community, where it spread.

All of the new attention on monkeypox has laid bare just how much scientists have yet to understand about the virus, McCollum says. "When this has all settled down, I think we'll have to think long and hard about where the research priorities are," she says.

By Max Kozlov

News explainer

HOW THE GIRAFFE GOT ITS NECK: 'UNICORN' FOSSIL COULD OFFER CLUES

A newly described species of ancient giraffoid had a thick helmet designed for fierce headbutting.

By Nicola Jones

How did the giraffe get its long neck? Researchers say that a giraffoid that lived millions of years ago in China could shed light on this puzzler. The animal, named after a mythical unicorn-like creature, had a thick headpiece optimized for high-speed head-bashing fights.

The giraffe's neck has intrigued researchers for decades. There should be a good reason for the extraordinary length, because it causes hardship. One prevailing theory is that giraffes evolved longer necks to reach higher trees for food. Another idea is that they evolved longer necks for sexual competition, with longer necks helping to attract mates and males engaging in violent neck-swinging fights. This theory is sometimes contested on the basis of the fact that males don't have longer necks than females. "It been very difficult for the traditional giraffe researchers to accept this sexual-selection idea," says Rob Simmons, a behavioural ecologist at the University of Cape Town in South Africa. The fossilized remains of the ancient giraffoid, described on 2 June (S.-Q. Wang *et al. Science* **376**, eabl8316; 2022), add more data to the debate.

Co-author Jin Meng first stumbled on a skull with four vertebrae lying on the sands of the Junggar Basin in northern China, back in 1996. "He cried: 'A strange beast!'," says Shi-Qi Wang, a palaeontologist at the Chinese Academy of Sciences Institute of Vertebrate Paleontology and Paleoanthropology in Beijing and an author of the study. Over two decades, Meng, Wang and their colleagues found more than 77 fossils of the same species, including another 2 skulls and some teeth. They describe the specimen as a previously unknown giraffe relative that lived in the Miocene, about 16.9 million years ago. It probably looked more like a short-necked African Okapi (*Okapia johnstoni*) than a giraffe, and had a 5-cm-thick hard structure on the top of its head, made of layers of keratin. They named the animal *Discokeryx xiezhi* after the *xiezhi*, a unicorn-like creature in Chinese mythology. Its complex head and neck-bone structure shows that it was "exquisitely adapted for power and strength to aid male–male combat", says Simmons.

Wang thinks that as ancestral giraffoids left the forest and entered grasslands, they fought ever-more fiercely with their necks, which grew longer as their fighting style evolved. But high foraging probably also had a role, he says.

However, palaeoungulate biologist Nikos Solounias at the New York Institute of Technology College of Osteopathic Medicine in Old Westbury is not convinced that the newly described headbutting ruminant is a particularly close relative of modern giraffes or can tell us much about their necks. "All ruminants fight with their horns and neck," he says. "Giraffes fight differently; they have a different evolutionary history." But Simmons argues that the work shows that sexual selection had a strong role in the neck shape of an ancestral giraffoid, which opens the door for it to be "equally likely" for modern giraffes.

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An artist's impression of *Discokeryx xiezhi*, which had a thick headpiece adapted for fighting.