

Medical News & Perspectives

Animal Reservoirs—Where the Next SARS-CoV-2 Variant Could Arise

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In April 2020, when hundreds of thousands of people worldwide had already succumbed to COVID-19, one infected individual—4-year-old **Nadia**—made global headlines. A Malayan tiger residing in New York's Bronx Zoo, Nadia was among the first animals known to have contracted the virus from a human, likely a caretaker.

Some animals infected with SARS-CoV-2 experience respiratory distress and life-threatening symptoms. Nadia survived, but others—including **Jupiter**, a tiger at Ohio's Columbus Zoo who died this past June—have not. And as with humans, even animals that remain asymptomatic may be capable of harboring and spreading the virus.

As of this May, 36 countries in Africa, the Americas, Asia, and Europe had **officially reported** SARS-CoV-2 infections in 23 non-human animal species, including not only big cats like tigers and lions but also domestic cats

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and dogs, gorillas, white-tailed deer, hamsters, farmed mink, otters, anteaters, manatees, hippopotamuses, and others, according to the World Organization for Animal Health, founded as OIE.

"With SARS-CoV-2, the remarkable thing is how many species have been infected with the human form of the virus," evolutionary biologist Edward Holmes, PhD, a professor at the University of Sydney, said in an interview.

Understanding how the virus jumps between species—known to ecologists as a "spillover" event—is complicated but potentially critical in ending the COVID-19 pandemic, Holmes and others told *JAMA*. Interspecies transmission can produce new animal reservoirs where the virus can multiply or persist for prolonged periods, creating the potential for the pathogen to transmit back to human populations.

As the virus jumps across species barriers, it also adapts to a range of different hosts, stockpiling mutations that can change its behavior, transmissibility, or ability to



evade vaccines and immune defenses in as-yet-unknown ways. "What we might fear is a situation where, when things seem like they're under control, we have a new variant that spreads fast, looks really different, and we don't know where it came from," Barbara Han, PhD, a disease ecologist at the Cary Institute of Ecosystem Studies in New York, said in an interview.

Without surveillance, new variants could go unnoticed. This past March, the World Health Organization, the OIE, and the United Nations' Food and Agriculture Organization (FAO) **called on all countries** to take steps to reduce SARS-CoV-2 transmission between humans and animals. The recommendations, aimed at protecting all species from illness and reducing the risk of new variants, emphasize monitoring mammalian wildlife for infection.

Looking beyond COVID-19, broader animal surveillance is needed to detect future zoonotic diseases before one of them causes the next pandemic, a possibility scientists say is heightened by a changing climate. "We are interacting more and more with wildlife in a planet undergoing climate change, and that will increase the

opportunities for viruses jumping between humans and animals," Holmes said. "It's an absolute certainty."

Many Hurdles

Evidence suggests that the novel coronavirus **likely originated in horseshoe bats** before being transmitted to a still-unknown intermediate host—pangolins and racoon dogs have been suspected, among others—that in turn passed it along to people, **possibly in 2 or more separate events**. That makes SARS-CoV-2 1 of **nearly 900 zoonotic pathogens** known to have made the leap from nonhuman animals to human populations over millennia.

Yet an infectious disease paradigm that places humans at the pinnacle of a chain of transmission is incorrect, according to Holmes. "Throughout history, humans have given our diseases to other animals," he said, referring to the concept of **reverse zoonosis**. "We're part of an ecosystem."

Despite this frequent exchange of viruses, certain factors are necessary for a pathogen to reach pandemic potential. For example, most pandemic-level viruses cause respiratory infections, and the risks

of a global outbreak are greater if—like SARS-CoV-2—they can be transmitted asymptomatically, Holmes said.

But even these stealth viruses must overcome additional hurdles that can prevent spillover into new species. The greatest barrier is a lock-and-key mechanism: the virus' surface antigens must be able to effectively bind host cell surface receptors to enter the cells and replicate. Minor differences in a virus surface protein's structure can prevent this "key" from unlocking the host's cellular machinery. In the case of SARS-CoV-2, its "key" is the spike protein and the "lock" is the angiotensin-converting enzyme 2 (ACE-2) receptor in humans and [hundreds of other vertebrates](#).

Different animals often have slight differences in their shared receptors. To bind them, viral proteins must undergo changes in their genetic sequence and resulting 3-dimensional structure. A few viruses, such as SARS-CoV-2, have the ability to rapidly tweak their keys to fit many locks. "SARS-CoV-2 is this kind of remarkable Swiss Army Knife type of virus that can use [ACE-2] receptors from a broad range of species," Washington State University's Michael Letko, PhD, a molecular virologist, said in an interview.

In a [study](#) last year, Angela Bosco-Lauth, PhD, DVM, a zoonotic diseases researcher at Colorado State University, and colleagues analyzed SARS-CoV-2 isolated from a small group of experimentally exposed mammals including cats and dogs. Sequencing these samples revealed 14 new variants, including 6 changes in the spike protein.

Other researchers have observed an increased evolutionary rate when the virus was first transmitted from humans to other species, including mink and white-tailed deer, according to Finlay Maguire, PhD, a genomic epidemiologist at Dalhousie University in Canada. "It's worrying because you have something that's adapted to one environment going into a different environment and then potentially changing quite a lot, quite quickly," Maguire said in an interview.

Fortunately for humans, Holmes said, that type of higher mutation rate typically helps viruses adapt to their new host and rarely confers an advantage to reinfecting the old one.

Prior to the COVID-19 pandemic, Letko and colleagues [studied](#) how Middle East respiratory syndrome coronavirus (MERS-

CoV), another zoonotic coronavirus, might have adapted to different hosts. In laboratory experiments, they repeatedly passaged the virus through a bat-derived version of the dipeptidyl peptidase 4 (DPP-4) host receptor, sequencing the virus' spike protein with every transmission event. Although at first the virus did not efficiently bind to this version of the DPP-4 receptor, the researchers found several different routes to adaptation—a spike mutation in 1 location vs 2 in another could yield similar improvements in the virus' binding ability.

The study was one of the first observations of the many ways a coronavirus could adapt to new hosts, Letko said. "At the time, it was a little strange to see," he said of the 2018 research. "But now it's what we see with SARS-CoV-2 and how these different variants are emerging."

He noted that MERS-CoV spike mutations improved the virus' interactions with the variant DPP-4 receptor but did not enhance its ability to bind to previously encountered forms. This is likely the case with SARS-CoV-2 variants, too. As the virus moves through animal species, it evolves to replicate in those species, not in humans. "As time goes on, it will maximize its potential for transmission in the other animal species," Holmes said. "Any variant that appears that is more transmissible and/or virulent in humans could only have evolved by chance."

Breaking Barriers

Experiments in the laboratory can reveal a virus' potential to jump between species and the sorts of variants it may spawn as it does so. "But we don't have the information to say whether or not it will spill over," Letko said. "That's where the ecological factors come into the picture."

Prime among those factors are human-animal interactions. Within the first 2 months of COVID-19's onset, researchers began to scrutinize domestic cats and dogs for infections, Samira Mubareka, MD, a clinical scientist at the University of Toronto's Sunnybrook Research Institute, said in an interview. In the pandemic's first year, mink infections were reported across farms in several countries, including the Netherlands, Canada, and the US, and some outbreaks led to mass culling.

To identify susceptible species and areas for surveillance, epidemiologists, wildlife

biologists, and others have homed in on animals that are likely to come into close contact with people in markets or agricultural settings.

"We try to pick species that are ecologically relevant," Bosco-Lauth said in an interview.

Certain wildlife species that live close to humans—striped skunks, deer mice, and bushy-tailed woodrats—are susceptible to SARS-CoV-2 infection and can shed the virus, Bosco-Lauth and colleagues [reported](#) in 2021. Other animals included in the study, such as cottontail rabbits, house mice, and raccoons, were resistant to infection.

In [another effort at surveillance](#), Mubareka and colleagues sampled 776 animals from 17 wildlife species in Ontario and Quebec, finding no evidence of current or prior infection. After SARS-CoV-2 infections in white-tailed deer were [reported](#) in the Midwestern US, however, Mubareka's team discovered infections in Canadian deer as well.

The researchers had launched a SARS-CoV-2 wildlife surveillance program in Ontario in the summer of 2020. The ongoing initiative, a collaboration with preexisting surveillance networks for rabies and chronic wasting disease, involves studying roadkill and trapping and performing live sampling of wild mink and other small animals. The program also relies on hunters to provide samples. For some species such as deer, "it's been more opportunistic sampling" because of difficulties with sampling live animals in the wild, Jeff Bowman, PhD, a wildlife ecologist at the Ontario Ministry of Natural Resources and Forestry, said in an interview.

This past May, the team reported the discovery of "the most divergent SARS-CoV-2 lineage to date" in white-tailed deer in Ontario. Comparison with viral genomes from human infections revealed that deer may have passed the variant to at least 1 person, according to a [preprint article](#) that has not yet been peer-reviewed. Farmed [mink](#) in the Netherlands and pet shop [hamsters](#) in Hong Kong also have infected humans. And this July, researchers in Thailand published a [case report](#) of a veterinarian infected by a sedated house cat that sneezed during a SARS-CoV-2 nasal swabbing.

Although such spillback events have been rare, this may not always be the case. Han likens the growing number of potential SARS-CoV-2 animal reservoirs to rolling more

dice in a game of chance. As the number of animal species infected with SARS-CoV-2 rises, so do the odds of new variants emerging and spilling back into humans. "It's like putting more dice out there to be rolled forever," she said. "You just never know when you might roll the combination that gives you the next Omicron."

Han is taking a computational approach to identify where these new variants might arise. Her team has developed a [machine learning model](#) to predict the most spillover-susceptible species. The technique accounts for not only species' ACE-2 sequence similarities but also nuances in real-world interactions and geographic distributions.

Such models need confirmation from laboratory studies and fieldwork surveillance. But they "can help prioritize where to conduct expensive surveillance," Han said. "They're predictions that are meant to be tested, and it's up to us to decide what level of testing we're willing to invest in."

The Climate Factor

Airborne transmission during close contact, virions in wastewater, and rodents and other small animals that live in proximity to humans all may play some role in cross-species SARS-CoV-2 infection, according to Mubareka. For white-tailed deer, the [potential culprits include](#) discarded used face masks or tissues, contaminated wastewater, intermediate animal hosts, or direct transmission from humans.

Containing the pandemic will require a deeper understanding of how these events occur and their impact on viral evolution. Distinct virus populations evolving in different

hosts could represent fundamental shifts in the ecology and evolution of SARS-CoV-2 and could result in different disease dynamics, Maguire said. For this reason, efforts to curb the ongoing pandemic—and future zoonotic threats—must focus not just on human public health measures but animal-focused surveillance and control measures as well.

Those measures are now more critical than ever, as habitat destruction, intensified agriculture to meet growing human needs, and illegal wildlife trade and hunting threaten to increase the likelihood of viruses jumping between species.

Although policy makers have emphasized the need to detect and quell emerging zoonotic threats, an approach that suggests action should be taken only after humans get sick is insufficient, researchers recently [argued](#) in *Science Advances*. Computing the global cost of pandemics in terms of human fatalities and economic impact, they estimated that efforts at primary prevention—spotting emerging viruses *before* they cause pandemics—“cost less than 1/20th the value of lives lost each year” to such threats.

That prevention relies on improving spillover surveillance, developing global databases of virus sequences, reducing deforestation, and better managing wildlife trade, according to the authors. Initiatives like the [Global Virome Project](#) encourage these types of preventive efforts.

One research team recently [simulated](#) how viral sharing between species might evolve over the next half century. As climate change alters human land use and

causes other species to shift their geographic ranges, the scientists predicted that animals would congregate in biodiversity hotspots, particularly at higher elevations. Those regions were predicted to overlap with areas of greater human population density, especially in Africa and Asia.

This shifting human-animal interface, which Holmes described as the “critical fault line” for zoonoses, is expected to drive about 4000 new cross-species viral transmissions based on projections for the year 2070. “This ecological transition may already be underway and holding warming under 2 °C within the century will not reduce future viral sharing,” the researchers wrote in an article published in *Nature* this past spring.

Such studies—and the current pandemic—emphasize the profound link between human and ecosystem health and the need to monitor and protect animals, Mubareka said: “Humans are one of many animal species, and the health of all animal species is interdependent. If we've learned anything from SARS-CoV-2, it's that if we want to prevent the next pandemic, then we really need to be proactive about surveillance because we're all connected.” ■

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Note: Source references are available through embedded hyperlinks in the article text online.