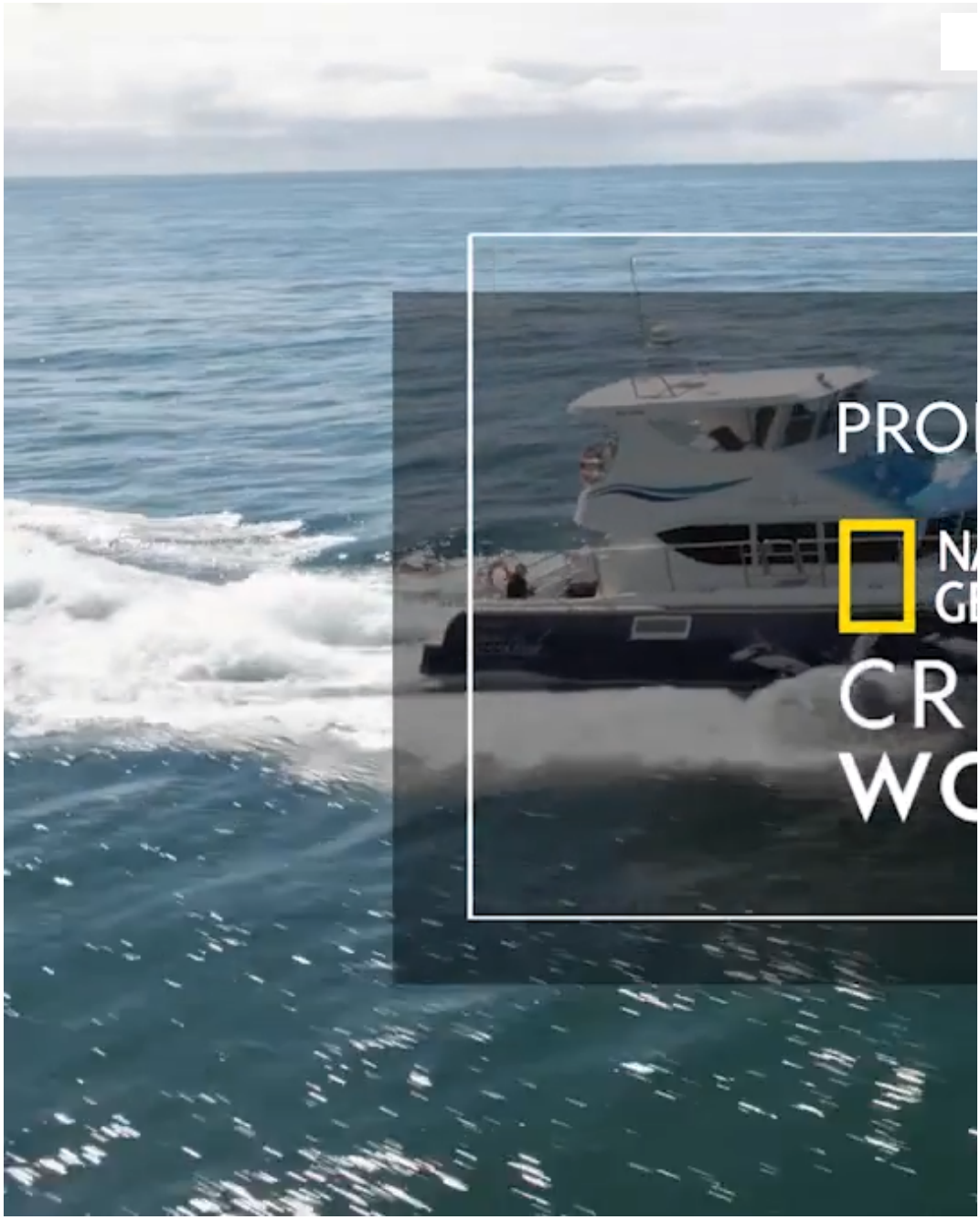
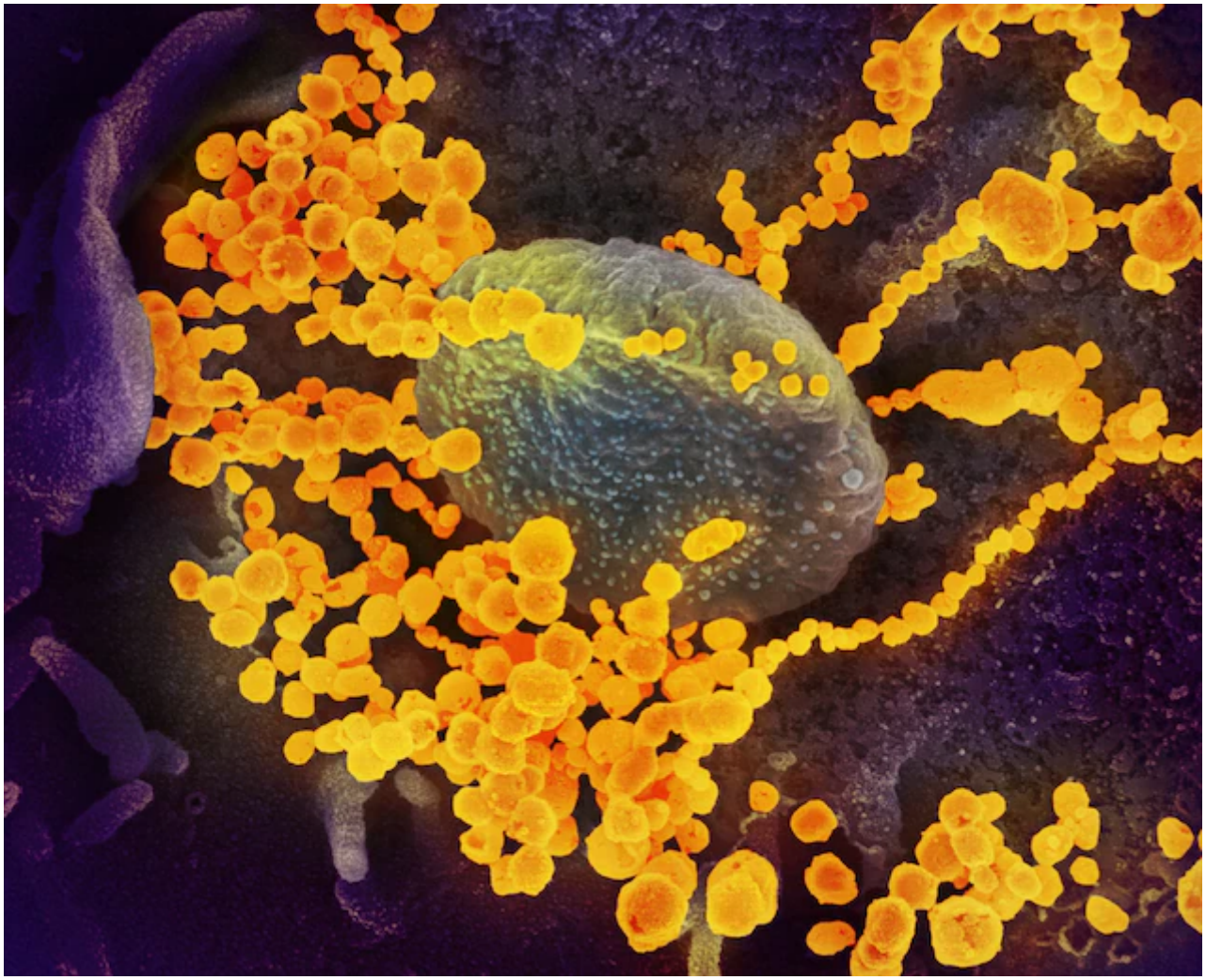




This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab. SARS-CoV-2 is the virus that causes COVID-19.
PHOTOGRAPH COURTESY NIAID-RML

SCIENCE CORONAVIRUS COVERAGE

There are more viruses than stars in the universe. Why do only some infect us?

BY **KATHERINE J. WU**

PUBLISHED APRIL 15, 2020 • 9 MIN READ

An estimated 10 nonillion (10 to the 31st power) individual viruses exist on our planet—enough to assign one to every star in the universe 100 million times over.

Viruses infiltrate every aspect of our natural world, seething in seawater, drifting through the atmosphere, and lurking in miniscule motes of soil. Generally considered non-living entities, these pathogens can only replicate with the help of a host, and they are capable of hijacking organisms from every branch of the tree of life—including a multitude of human cells.

Yet, most of the time, our species manages to live in this virus-filled world relatively free of illness. The reason has less to do with the human body's resilience to disease than the biological quirks of viruses themselves, says Sara Sawyer, a virologist and disease ecologist at the University of Colorado Boulder. These pathogens are extraordinarily picky about the cells they infect, and only an infinitesimally small fraction of the viruses that surround us actually pose any threat to humans.

Still, as the ongoing COVID-19 pandemic clearly demonstrates, outbreaks of new human viruses do happen—and they aren't as unexpected as they might seem.

To better forecast and prevent outbreaks, scientists are homing in on the traits that may explain why some viruses, and not others, can make the hop into humans. Some mutate more frequently, perhaps easing their

When it comes to epidemics, “there are actually patterns there,” says Raina Plowright, a disease ecologist at Montana State University. “And they are predictable patterns.”

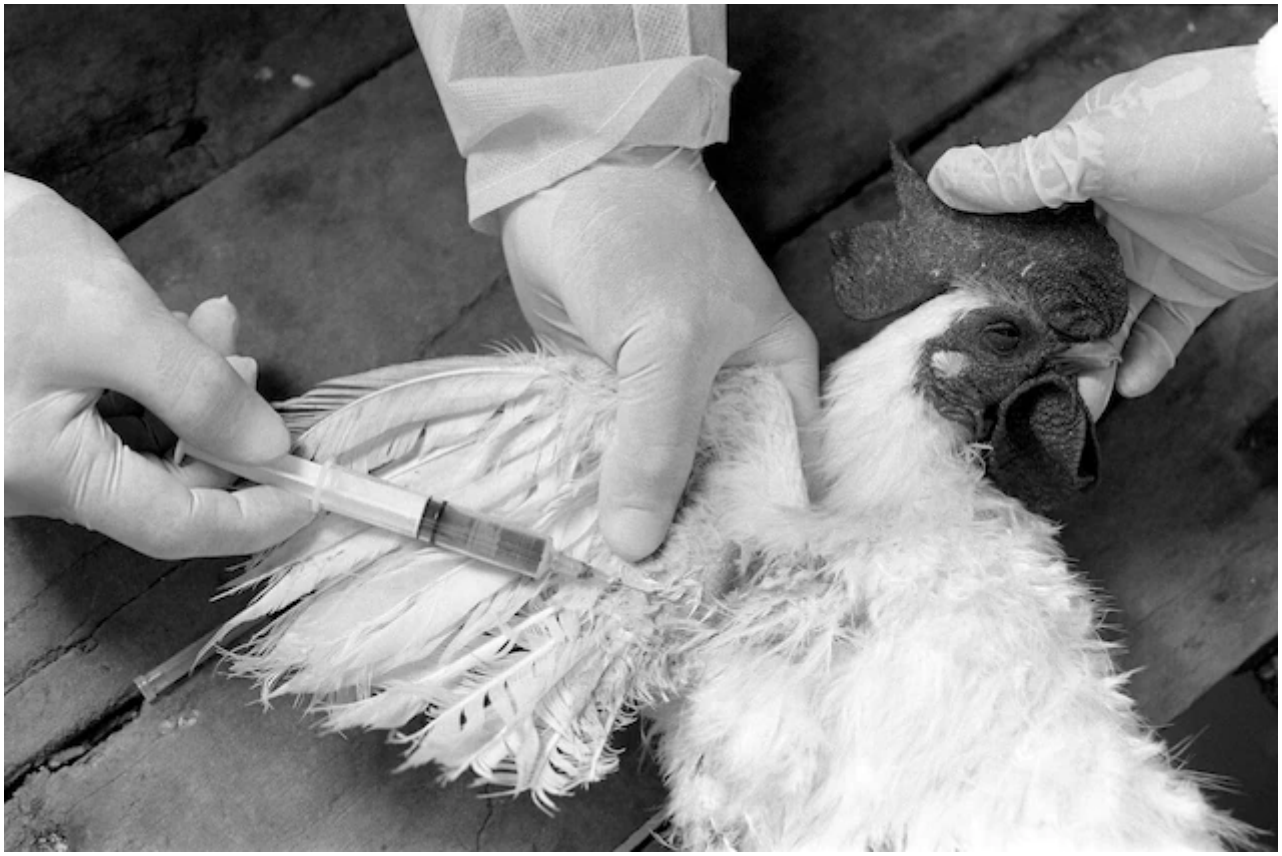
Crossing the species divide

Most new infectious illnesses enter the human population the same way COVID-19 did: as a zoonosis, or a disease that infects people by way of an animal. Mammals and birds alone are thought to host about 1.7 million undiscovered types of viruses—a number that has spurred scientists around the world to survey Earth’s wildlife for the cause of our species’ next pandemic. (Bacteria, fungi, and parasites can also pass from animals to people, but these pathogens can typically reproduce without infecting hosts, and many viruses are better equipped to cross species.)

To make a successful transition from one species to another, a virus must clear a series of biological hurdles. The pathogen has to exit one animal and come into contact with another, then establish an infection in the second host, says Jemma Geoghegan, a virologist at Macquarie University. This is known as a spillover event. After the virus has set up shop in a new host, it then needs to spread to other members of that species.

Exact numbers are hard to estimate, but the vast majority of animal-to-

ecologist at Stanford University.



Inspectors take a blood sample from a chicken to test for avian flu in Can Tho, Vietnam.
PHOTOGRAPH BY LYNN JOHNSON, NAT GEO IMAGE COLLECTION

Those factors include how often a virus-carrying animal encounters humans, the means through which a virus is spread, how long a virus can persist outside of a host, and how efficiently a virus can subvert the human immune system. A wrinkle at any step along the chain of transmission could foil the pathogen's attempt to infect a new species. Even factors that seem innocuous—like above-average rainfall, or a local food shortage—can rejigger the dynamics of how humans and animals interact.

For a virus, one of most challenging aspects of transmission is gaining entry to a new host's cells, which contain the molecular machinery that these pathogens need to replicate. This process typically involves a virus latching on to a molecule that studs the outside of a human cell—a bit like a key clicking into a lock. The better the fit, the more likely the pathogen is to access the cell's interior. SARS-CoV-2, the coronavirus that causes COVID-19, engages with the protein ACE2 to enter cells in the human airway.

For any given host, "there's a very small number of pathogens that are able to" break into its cells this way, Sawyer says. The vast majority of the viruses we encounter simply bounce off our cells, eventually exiting our bodies as harmless visitors.

The many faces of viruses

Sometimes, however, a pathogen manages to slip through. More than 200 viruses are known to cause disease in humans, and all are capable of breaking into human cells. But they almost certainly didn't start out with that ability.

The host molecules that viruses glom on to, which are called receptors, tend to be highly variable from one species to the next, Sawyer says. "A key property of a virus that can accomplish a zoonosis is that it can, with a small number of evolutionary steps, adapt to use the human version of that receptor."

Viruses with a lot of genetic flexibility, and particularly those that encode their genomes as RNA rather than DNA, are well-suited to crossing the

introducing mutations at a high rate. This error-prone process creates an immense amount of diversity into populations of RNA viruses, allowing them to adapt to new environments—including new host species—at a rapid pace, says Sarah Zohdy, a disease ecologist at Auburn University.

Of the pathogens that have infected the human population in recent decades, the majority have been RNA viruses, including Ebola, SARS, MERS, Zika, several influenza viruses, and SARS-CoV-2.

Some viruses can also change up their genetic code through a second method that's a bit like sexual reproduction. When two genetically dissimilar viruses infect the same cell, they may swap segments of their genomes with each other as they replicate, yielding hybrid viruses that differ from both their "parents." Flu viruses, which rely on RNA, are among those that both mutate independently and frequently mingle their genomes—traits that have helped influenza shuttle back and forth between an entire menagerie of wild and domestic species, including pigs, whales, horses, seals, several types of birds, and, of course, humans.

The "perfect" pathogen

Neither mutation nor viral interbreeding, however, can guarantee spillover—and viruses that lack one or both traits can still infect a wide range of hosts.

A few years ago, Geoghegan and her colleagues identified a slew of other

for long periods of time without being lethal. Lengthier infections, she says, likely give these stealthy pathogens more time to adapt and spread to new species.

Many of the pathogens that jump into people do so from rodents, bats, and non-human primates, likely due to some combination of these species' abundance, proximity to people, and biological similarities to humans, Zohdy says. And of course, viruses related to known human pathogens, such as new strains of influenza and the novel coronavirus, are always possible threats. Although many of these microbes end up being harmless to humans, a handful of genetic changes can make them compatible with our cells.

Viral traits alone aren't enough to predict pandemics. But as scientists continue to catalog the diverse viruses that inhabit our planet, knowing some of these telltale traits can help them prioritize pathogens for further study, says Tracey Goldstein, associate director of the University of California, Davis' One Health Institute. After a candidate virus is identified

Traditionally, many of these steps have been performed by different groups of researchers, with some focusing their efforts on sampling viruses in the wild, and others sticking mostly to characterizing pathogens in the lab, Tovar says. However, scientists can't get a full picture of the pathogens that could put us at risk without surveillance in the field, and they can't confirm which ones pose the biggest threats without laboratory experiments.

"So many things need to come together, and it all matters," Plowright says. But this complexity can work in humans' favor: The more spillover factors that researchers identify, the more opportunities they have to intervene. Eventually, with enough information, we might even be able to stop outbreaks before they occur.

"The amount of information we've been able to get in such a short period of time ... is incredible," Zohdy says. "That's already giving me hope."

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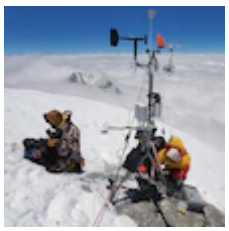

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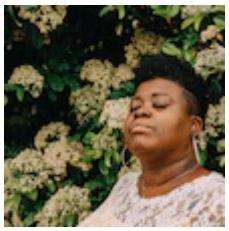

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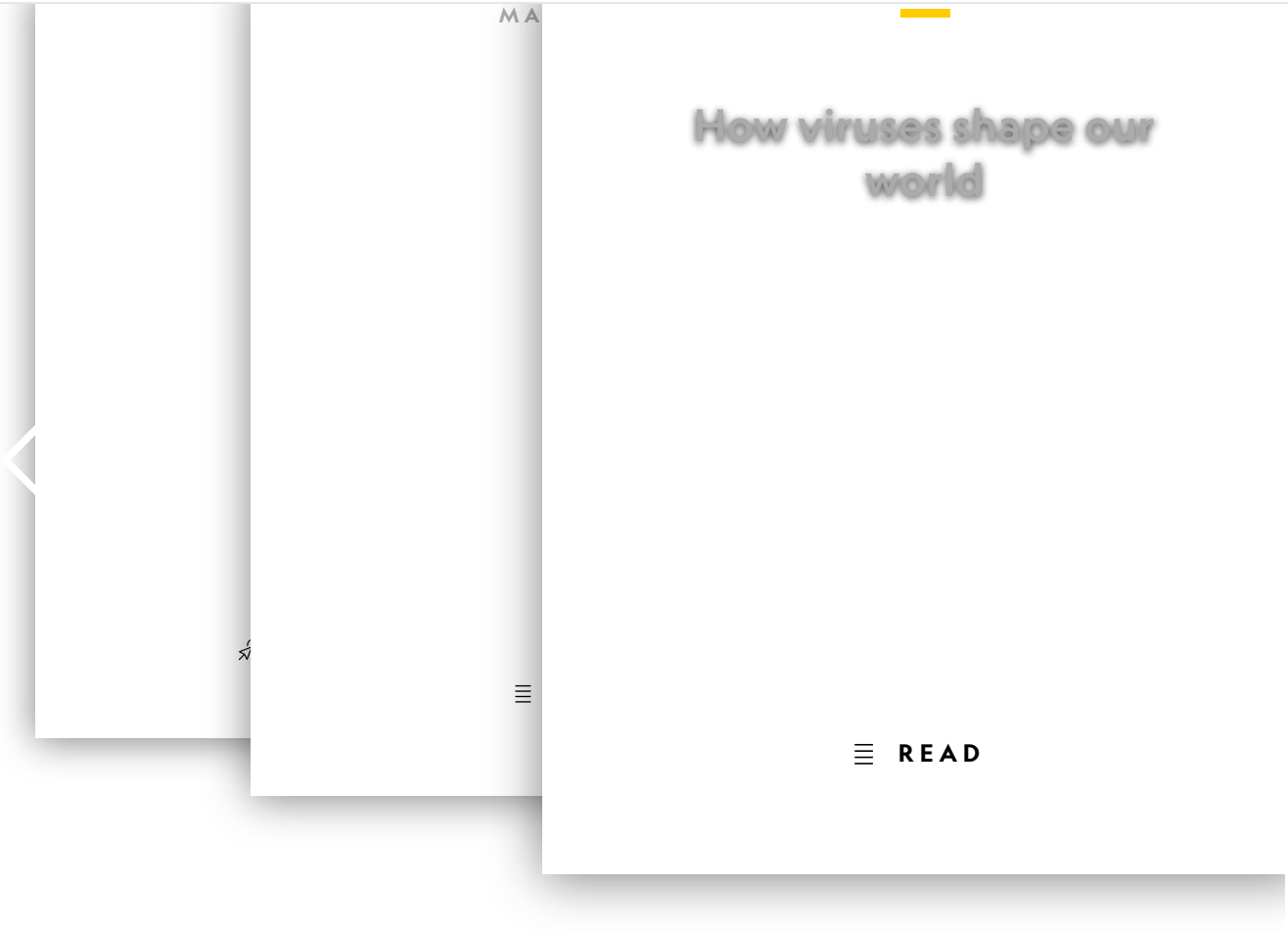

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