

Characteristics that Give Viruses Pandemic Potential

A handful of factors tip the scales in making a virus more likely to trigger a disruptive global outbreak. Right now, scientists tend to rank influenza, coronaviruses, and Nipah virus as the biggest threats.



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Even before COVID-19 swept across the globe this year, coronaviruses were on scientists' radar as pathogens that could one day ignite a pandemic. They'd threatened to before—in 2002–03, the SARS virus infected 8,000 people in more than two dozen countries and killed almost 800—and they checked off several specific boxes that emerging infectious disease specialists worry about in a virus. But they're not the only group of viruses that researchers are concerned about. Influenza and a handful of other viruses have long been viewed as pandemic threats.

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One aspect that signals pandemic potential in a virus is having an RNA, rather than DNA, genome. That's because the process of copying RNA typically doesn't include a proofreader like DNA replication does, and so RNA viruses have higher mutation rates than the DNA variety. "This means they can change and become more adaptable to human infection and human transmission," says [Steve Luby](#), an epidemiologist at Stanford University.

Researchers on the lookout for dangerous pathogens also pay close attention to viruses with track records of leaping from animals to people. [Smallpox](#), [measles](#), Ebola, and HIV all originated in animals, as Luby estimates that 80 percent of our most devastating infections did.

Once a virus makes the zoonotic leap from animals to humans, it must then transmit from one person to the next if it is to cause an epidemic. In this respect, SARS-CoV-2 seems to outperform the original and deadlier SARS coronavirus, MERS coronavirus, and some bird flu strains. But these less-transmissible viruses could always acquire some new mutation that revs

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—Ralph Baric, University of North Carolina, Chapel Hill

up their R_0 , the expected number of infections caused by one person, increasing their potential to spread rapidly through human populations, says [Raina Plowright](#), an infectious disease researcher at Montana State University.

How a virus is transmitted is yet another consideration when evaluating its pandemic potential. The most concerning situation is when a virus can spread through respiratory droplets, allowing it to jump from person to person through close interactions, as is the case for the seasonal flu and also SARS-CoV-2. “An RNA virus that causes respiratory tract infections can evolve into something we haven’t seen before and spread rapidly,” says [Ralph Baric](#), a virologist at the University of North Carolina, Chapel Hill. Measles, an RNA paramyxovirus spread through respiratory secretions, is perhaps the most contagious disease known in humans.

As the world continues to grapple with SARS-CoV-2, *The Scientist* asked virologists to rank viruses with the greatest potential to cause a future pandemic. Three answers routinely popped up: influenza, coronaviruses, and paramyxoviruses, a large family of viruses that includes mumps and respiratory syncytial virus (RSV), as well as Nipah virus, which researchers say poses the biggest pandemic threat among them. “There are lots of concerns to keep communicable disease epidemiologists up at night,” says Luby.

Influenza

Prior to the SARS-CoV-2 outbreak, most virologists rated influenza as the most likely agent to trigger a deadly pandemic. [The 1918 flu pandemic](#) caused an estimated 50 million to 100 million deaths over two years, and there have been three flu pandemics since—in [1957–58](#), [in 1968](#), and most recently [in 2009](#).

Influenza is an RNA virus and thus prone to mutation, which necessitates a new seasonal flu vaccine each year. Virologists classify influenza strains according to two surface proteins: the hemagglutinin (H) protein that binds to a receptor on target cells and the neuraminidase (N) protein that virus particles use to escape host cells. There are 18 hemagglutinin subtypes and 11 neuraminidase subtypes. It’s likely that all permutations occur influenza viruses that affect in influenza viruses that affect birds but only a handful have cropped up in those that infect people. “Over the last one hundred or so years, we have had pandemics and seasonal epidemics caused by only three of the eighteen H subtypes and two of the eleven N subtypes,” says virologist [Kanta Subbarao](#), director of the World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza in Melbourne.

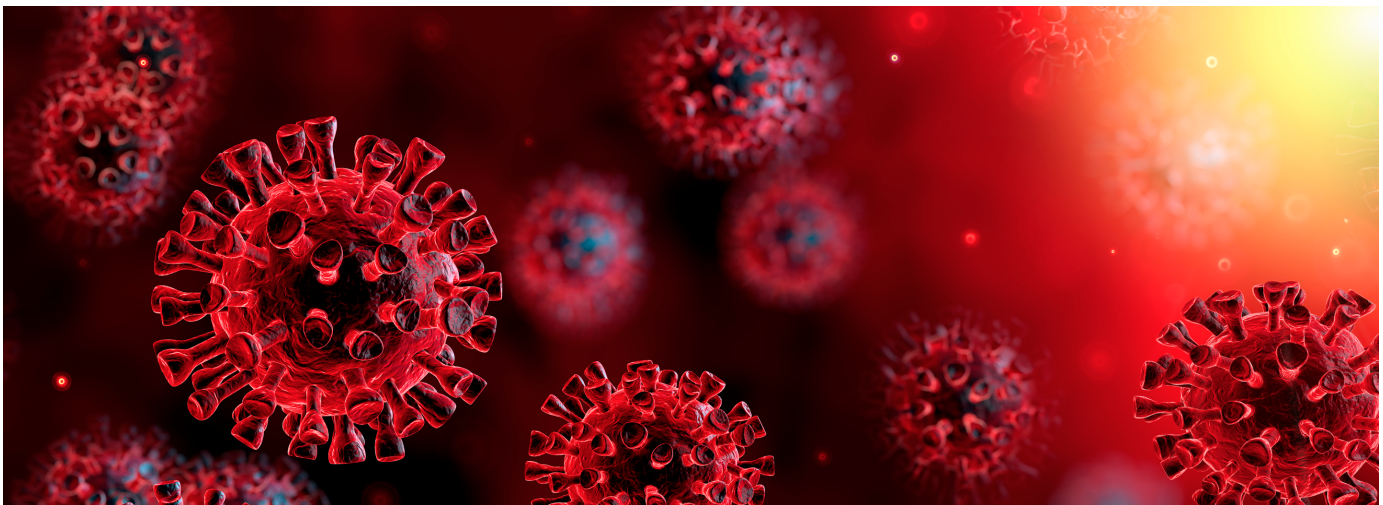
From time to time, influenza viruses in ducks and shorebirds spill over to infect domestic poultry and sometimes pigs. The H protein is critical. Concern mounts whenever the H protein of a bird flu virus gains the ability to infect human cells. This allows the virus to jump to humans, introducing people to a new strain with avian proteins to which they have little or no immunity. So far, says Luby, “the H7N9 and H5N1 viruses still primarily connect to the cellular receptors in birds, but

sometimes they infect people and cause serious disease.”

The concern is that some of the viruses with killer characteristics might change in a way that allows them to more easily spread from person to person. Indeed, influenza has a radical way to shapeshift. Its RNA genome is split into eight segments. When two different subtypes of virus, be they bird or mammalian strains, are in one cell, viral segments can be shuffled to create entirely new strains. Pigs are suspected to be ideal viral melting pots. “Pigs carry similar receptors to humans, and they can be infected by avian and mammalian viruses,” says Subbarao. “The 1957 and 1968 flu pandemics were caused by reassortant viruses, with some gene segments from avian influenza viruses and other segments from circulating human flu viruses. It is long proposed that this [mixing] happened in an intermediate host, possibly pigs.”

The WHO has a [constellation of national labs](#) to watch for emerging strains of flu, and now collaborates closely with the [World Organisation for Animal Health](#). “We want to pick up any novel influenza viruses in animals,” Subbarao explains. Scientists recently became concerned, for example, when a swine influenza variant of H1N1, [called G4](#), circulating in pigs was shown to be able to infect and replicate in human epithelial cells. The virus carries genes from the H1N1 subtype that caused the 2009 flu pandemic.

Pandemic pathogens are rare, however, and are by their nature difficult to predict. “We do know there are some things we should worry about,” Luby says, yet “we tend to get caught off guard.”



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Coronavirus

Both the SARS and MERS coronaviruses are deadlier than SARS-CoV-2. Fortunately, human-to-human transmission of SARS and MERS is relatively low. But there is a tremendous diversity of coronaviruses in bat species. They mostly infect the gut, but can replicate in lung tissue as well. After the [SARS outbreak](#) in 2002–03, scientists searched for coronaviruses in bats in Chinese caves and [found a trove of them](#) in common insectivorous species. Moreover, antibodies identified in the blood

of [people in southern China](#) suggest that some human populations are routinely exposed to bat coronaviruses. This gives the viruses ample opportunity to adapt to people.

Harbingers of coronaviruses' propensity to jump to new species are the lethal outbreaks that often occur on farms. Three devastating swine coronavirus strains have emerged in pigs in the last couple of decades. "These viruses are on the move," says Baric. He worries that we have "toggled on a switch" to promote coronavirus emergence from animal reservoirs into other mammalian species, including ourselves. This is mostly linked to human behavior, such as consumption and farming of wild animals in certain countries. "Markets where lots of animals are in cages together can mean more animal transmission and more humans getting infected," says Luby, who says he believes China should close all its wet markets.

The current coronavirus pandemic along with the first SARS outbreak are not the first we have experienced. MERS coronavirus seems to have been in camels for decades, occasionally infecting people. It has now caused 2,400 cases, mostly in the [Arabian Peninsula](#). Some virologists say that the coronaviruses that are now [endemic in people](#), causing common cold symptoms, may have sparked deadly pandemics when they first made the jump from animals to humans. The OC43 coronavirus, for example, seems to have come from bats via cattle and there is evidence that it caused a pandemic in the 1890s, says Baric.

Our immediate highest risk is coronaviruses.

—Steve Luby, Stanford University

Now, with the ongoing COVID-19 pandemic, some researchers rank coronaviruses as the biggest threat. "I'd put coronavirus ahead of flu," says Luby. "It demonstrated higher case fatality—not with SARS-CoV-2, but we have seen it with SARS and MERS," and it looks like the live markets in China are allowing coronaviruses associated with bats to spread to other mammals. "Our immediate highest risk is coronaviruses."

Nipah virus

In 1994, a mysterious disease broke out in horses in a suburb of Brisbane, Australia, called Hendra. Twenty-one horses fell severely ill from a pathogen that was soon named Hendra virus. Then, a vet attending to the sick horses died from the virus, whose origin was traced to fruit bats in the genus *Pteropus* (aka, flying foxes). Four years later, a related virus called Nipah virus was identified as the cause of an outbreak among pig farmers in Malaysia. Two million infected pigs were slaughtered, halting the outbreak. In 2001, researchers realized that outbreaks of Nipah virus in people happened each year [in Bangladesh](#), primarily from people drinking the sap of date trees that was contaminated with bat urine. But there didn't appear to be human-to-human transmission.

In 2018, however, [an outbreak in southern India](#) suggested that human-to-human transmission of Nipah virus was possible through close contact. [A 27-year-old villager](#), who may have contracted the

virus from fruit contaminated by bat saliva or urine, was admitted to the hospital in Kerala state and infected nine other people, including fellow patients, visiting relatives, and medical staff. He was referred to another hospital, where more patients and medical workers were infected. Twenty-one of the 23 infected people died from severe respiratory sickness and/or brain inflammation. “One reason it doesn’t take off is because it makes people so sick so quickly that they tend to be hospitalized and isolated,” says Plowright, who studies bats and Nipah virus outbreaks. But Nipah virus’s fatality rate of between 50 percent and 100 percent is exactly what makes it such a concern.

Nipah and Hendra belong to a group of paramyxoviruses now called henipavirus, and there are many more strains harbored in flying foxes in Asia, Oceania, and Africa, says Plowright. Although henipaviruses have not yet caused widespread outbreaks in people, other paramyxoviruses, such as measles and mumps, have. “Some of these viruses spread really well,” says [Rebecca Dutch](#), a molecular biologist at the University of Kentucky. If Nipah moved efficiently from one person to another, perhaps mutating so it transmits before making someone really sick, “this would be devastating,” says Luby, “more like the Black Plague.”



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Other potential threats

Viruses that did not top the list but still demand attention are filoviruses such as [Ebola and Marburg virus](#), which cause hemorrhagic fever and can infect apes, monkeys, and bats, in addition to humans. “The fact that Ebola requires blood or body fluids to be transmitted means that it is harder to transmit and so less likely to be a global threat,” explains Luby. And as with Nipah virus infections, people get sick quickly and thus are isolated early. For a filovirus to cause a pandemic, it would need to be transmissible in respiratory form or spread readily in diarrhea, experts say, and it’s not yet clear how easily that might happen. “The big question is, what is the diversity of the Ebola viruses in nature?” says Baric.

Other viruses that scientists are keeping tabs on include those in the [Bunyavirus](#) and [Arenavirus](#) families, which primarily infect rodents, and mosquito-transmitted [dengue](#), [Zika virus](#), and [West](#)

Nile virus. “Vector-borne pathogens have the potential to infect two billion people,” says Baric, “but if you are in the northern latitudes it may be low risk for you.” As the geographical range of mosquitoes **spreads to higher latitudes** with climate change, however, so too will the diversity of the pathogens they carry.

There is also “**disease X**.” The WHO uses this term to acknowledge that a serious epidemic could be caused by a pathogen currently unknown to cause human disease. But studying an undescribed pathogen is a tall order. “Until SARS emerged in 2002, those who study coronaviruses had trouble getting anyone to fund their research,” says Dutch. “There certainly could be things out there we don’t know about.”

Experts warn that humans are creating conditions for more viral spillover events by disrupting natural habitats and by packing different wild animals together in wildlife markets. “We are creating the perfect storm for new viruses to emerge,” says Plowright, who recently coauthored a **review** on bat-borne virus diversity, spillover, and emergence. Despite this, the scientific community is largely unable to accurately forecast future outbreaks, she adds. “No one predicted that a flu pandemic [2009] would come from pigs in Mexico,” says Plowright. “We have to keep an open mind as to what the next pathogen outbreak is going to be.”

But researchers are hopeful that our experience with COVID-19 will turn the tide of pandemic preparedness. As Luby says, “I anticipate there will be more attention to these threats.”

Viruses that Threaten to Spark Another Pandemic

Characteristics	Coronaviruses	Influenza	Paramyxoviruses (henipaviruses)
Animal reservoirs	<p>Huge diversity in insectivorous bats and fruit-eating bats. Horseshoe bats (genus <i>Rhinolophus</i>) in Southeast Asia harbor SARS-like coronaviruses.</p>	<p>Water birds, poultry, and domestic pigs. Some outbreaks in dogs and horses.</p>	<p>Some family members abundant in fruit bats.</p>
Spillover history	<p>Four “common cold” coronaviruses may have origins in bats, possibly in last few centuries. SARS caused an outbreak during 2003–04. MERS continues to infect people, presumably jumping from camels.</p>	<p>Numerous pandemics throughout human history were likely due to flu. Confirmed flu pandemics include the devastating 1918 pandemic, as well as pandemics in 1957–58, 1969, and 2009.</p>	<p>Hendra virus infected horses and people first in 1994. Nipah virus first recorded in pigs and humans in 1998.</p>
Case fatality rate	<p>Varies hugely. COVID-19 possibly around 1 percent. SARS is thought to be closer to 15 percent. MERS has proved fatal in about 35 percent of patients.</p>	<p>In the case of the 1918 pandemic, the case fatality rate was around 2.5 percent globally.</p>	<p>Some of the deadliest known pathogens. Hendra virus rarely infects humans, but when it does, the fatality rate is around 50 percent. The case fatality rate for Nipah is even higher, ranging from 50 percent to 100 percent.</p>

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coronavirus, COVID-19, disease & medicine, feature, infectious disease, influenza, Nipah virus, outbreak, pandemic, reservoir, SARS-CoV-2, viral reservoir, virus, virus evolution