

From Bats to Human Lungs, the Evolution of a Coronavirus

By Carolyn Kormann
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A detailed illustration of the coronavirus.

Illustrations by Laura Edelbacher; Animation by Patryk Senwicki

For thousands of years, a parasite with no name lived happily among horseshoe bats in southern China. The bats had evolved to the point that they did not notice; they went about their nightly flights unbothered. One day, the parasite—an ancestor of the coronavirus, SARS-CoV-2—had an opportunity to expand its realm. Perhaps it was a pangolin, the scaly anteater, an endangered species that is a victim of incessant wildlife trafficking and sold, often secretly, in live-animal markets throughout Southeast Asia and China. Or not. The genetic pathway remains unclear. But to survive in a new species, whatever it was, the virus had to mutate dramatically. It might even have taken a segment of a different coronavirus strain that already inhabited its new host, and morphed into a hybrid—a better, stronger version of itself, a pathogenic Everyman capable of thriving in diverse species. More recently, the coronavirus found a new species: ours. Perhaps a weary traveller rubbed his eyes, or scratched his nose, or was anxiously, unconsciously, biting his fingernails. One tiny, invisible blob of virus. One human face. And here we are, battling a global pandemic.

The world's confirmed cases (those with a positive lab test for COVID-19, the disease caused by SARS-CoV-2) doubled in seven days, from nearly two hundred and thirteen thousand, on March 19th, to four hundred and sixty-seven thousand, on March 26th. Nearly twenty-one thousand people have died. The United States now has more confirmed cases than any country on earth, with more than eighty thousand on March 26th. These numbers are a fraction of the real, unknown total in this country and around the world, and the numbers will keep going up. Scientists behind a new study, published earlier this month in the journal *Science*, have found that for every confirmed case there are likely five to ten more people in the

community with an undetected infection. This will likely remain the case. “The testing is not near adequate,” one of the study’s authors, Jeffrey Shaman, an environmental-health sciences professor at Columbia University, said. Comments from emergency-room doctors have been circulating on social media like S.O.S. flares. One, from Daniele Macchini, a doctor in Bergamo, north of Milan, described the situation as a “tsunami that has overwhelmed us.”

Scientists first discovered that coronaviruses originate among bats following the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003. Jonathan Epstein, an epidemiologist at the EcoHealth Alliance in New York who studies zoonotic viruses—those that can jump from animals to people—was part of a research team that went hunting for the source in China’s Guangdong Province, where simultaneous SARS outbreaks had occurred, suggesting multiple spillovers from animals to people. At first, health officials believed palm civets, a mongoose-like species commonly eaten in parts of China, were responsible, as they were widely sold at markets connected to the SARS outbreak, and tested positive for the virus. But civets bred elsewhere in Guangdong had no antibodies for the virus, indicating that the market animals were only an intermediary, highly infectious host. Epstein and others suspected that bats, which are ubiquitous in the area’s rural, agricultural hills, and were, at the time, also sold from cages at Guangdong’s wet markets, might be the coronavirus’s natural reservoir.

The researchers travelled through the countryside, setting up field labs inside limestone caverns and taking swabs from dozens of bats through the night. After months of investigation, Epstein’s team discovered four species of horseshoe bats that carried coronaviruses similar to SARS, one of which carried a coronavirus that was, genetically, a more than ninety per cent match. “They were found in all of the locations where SARS clusters were happening,” he said.

After years of further bat surveillance, researchers eventually found the direct coronavirus antecedent to SARS, as well as hundreds of other coronaviruses circulating among some of the fourteen hundred bats species that live on six continents. Coronaviruses, and other virus families, it turns out,

have been co-evolving with bats for the entire span of human civilization, and possibly much longer. As the coronavirus family grows, different strains simultaneously co-infect individual bats, turning their little bodies into virus blenders, creating new strains of every sort, some more powerful than others. This process happens without making bats sick—a phenomenon that scientists have linked to bats’ singular ability, among mammals, to fly. The feat takes a severe toll, such that their immune systems have evolved a better way to repair cell damage and to fight off viruses without provoking further inflammation. But when these viruses leap into a new species—whether a pangolin or a civet or a human—the result can be severe, sometimes deadly, sickness.

In 2013, Epstein’s main collaborator in China, Shi Zheng-Li, sequenced a coronavirus found in bats, which, in January, she discovered shares ninety-six per cent of its genome with SARS-CoV-2. The two viruses have a common ancestor that dates back thirty to fifty years, but the absence of a perfect match suggests that further mutation took place in other bat colonies, and then in an intermediate host. When forty-one severe cases of pneumonia were first announced in Wuhan, in December, many of them were connected to a wet market with a notorious wildlife section. Animals are stacked in cages—rabbits on top of civets on top of ferret-badgers. “That’s just a gravitational exchange of fecal matter and viruses,” Epstein said. Chinese authorities reported that they tested animals at the market—all of which came back negative—but they have not specified which animals they tested, information that is crucial for Epstein’s detective work. Authorities later found the virus in samples taken from the market’s tables and gutters. But, because not all of the first patients were tied to the market, nor were they connected to one another, Epstein said, “it raised the question of, well, perhaps those forty-one weren’t the first cases.”

Analyses of the SARS-CoV-2 genome indicate a single spillover event, meaning the virus jumped only once from an animal to a person, which makes it likely that the virus was circulating among people before December. Unless more information about the animals at the Wuhan market is released, the transmission chain may never be clear. There are, however, numerous possibilities. A bat hunter or a

wildlife trafficker might have brought the virus to the market. Pangolins happen to carry a coronavirus, which they might have picked up from bats years ago, and which is, in one crucial part of its genome, virtually identical to SARS-CoV-2. But no one has yet found evidence that pangolins were at the Wuhan market, or even that vendors there trafficked pangolins. “We’ve created circumstances in our world somehow that allows for these viruses, which would otherwise not be known to cause any problems, to get into human populations,” Mark Denison, the director of pediatric infectious diseases at Vanderbilt University Medical Center’s Institute for Infection, Immunology, and Inflammation, told me. “And this one happened to say, ‘I really like it here.’”

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Caption: According to researchers at Rocky Mountain Laboratories, some viral particles remain viable up to four hours on copper, twenty-four hours on cardboard, and seventy-two hours on plastic and stainless steel, though the number of viable particles begins to decrease within minutes.

The new coronavirus is an elusive killer. Since people have never seen this strain before, there is much about it that remains a mystery. But, in just the past few weeks, genetic sleuthing, atomic-level imaging, computer modelling, and prior research on other types of coronaviruses, including SARS and MERS (Middle East Respiratory Syndrome), have helped researchers to quickly learn an extraordinary amount—particularly what might treat or eradicate it, through social-distancing measures, antiviral drugs, and, eventually, a vaccine. Since January, nearly eight hundred papers about the virus have been posted on BIORxiv, a preprint server for studies that have not yet been peer-reviewed. More than a thousand coronavirus genome sequences, from different cases around the world, have been shared in public databases. “It’s insane,” Kristian Andersen, a professor in the Department of Immunology and Microbiology at Scripps Research, told me. “Almost the entire scientific field is focussed on this virus now. We’re talking about a warlike situation.”

There are endless viruses in our midst, made either of RNA or DNA. DNA viruses, which exist in much greater abundance around the planet, are capable of causing systemic diseases that are endemic,

latent, and persistent—like the herpes viruses (which includes chicken pox), hepatitis B, and the papilloma viruses that cause cancer. “DNA viruses are the ones that live with us and stay with us,” Denison said. “They’re lifelong.” Retroviruses, like H.I.V., have RNA in their genomes but behave like DNA viruses in the host. RNA viruses, on the other hand, have simpler structures and mutate rapidly. “Viruses mutate quickly, and they can retain advantageous traits,” Epstein told me. “A virus that’s more promiscuous, more generalist, that can inhabit and propagate in lots of other hosts ultimately has a better chance of surviving.” They also tend to cause epidemics—such as measles, Ebola, Zika, and a raft of respiratory infections, including influenza and coronaviruses. Paul Turner, a Rachel Carson professor of ecology and evolutionary biology at Yale University, told me, “They’re the ones that surprise us the most and do the most damage.”

Scientists discovered the coronavirus family in the nineteen-fifties, while peering through early electron microscopes at samples taken from chickens suffering from infectious bronchitis. The coronavirus’s RNA, its genetic code, is swathed in three different kinds of proteins, one of which decorates the virus’s surface with mushroom-like spikes, giving the virus the eponymous appearance of a crown. Scientists found other coronaviruses that caused disease in pigs and cows, and then, in the mid-nineteen-sixties, two more that caused a common cold in people. (Later, widespread screening identified two more human coronaviruses, responsible for colds.) These four common-cold viruses might have come, long ago, from animals, but they are now entirely human viruses, responsible for fifteen to thirty per cent of the seasonal colds in a given year. We are their natural reservoir, just as bats are the natural reservoir for hundreds of other coronaviruses. But, since they did not seem to cause severe disease, they were mostly ignored. In 2003, a conference for nidovirales (the taxonomic order under which coronaviruses fall) was nearly cancelled, due to lack of interest. Then SARS emerged, leaping from bats to civets to people. The conference sold out.

SARS is closely related to the new virus we currently face. Whereas common-cold coronaviruses tend to infect only the upper respiratory tract (mainly the nose and throat), making them highly contagious,

SARS primarily infects the lower respiratory system (the lungs), and therefore causes a much more lethal disease, with a fatality rate of approximately ten per cent. (MERS, which emerged in Saudi Arabia, in 2012, and was transmitted from bats to camels to people, also caused severe disease in the lower respiratory system, with a thirty-seven per cent fatality rate.) SARS-CoV-2 behaves like a monstrous mutant hybrid of all the human coronaviruses that came before it. It can infect and replicate throughout our airways. “That’s why it is so bad,” Stanley Perlman, a professor of microbiology and immunology who has been studying coronaviruses for more than three decades, told me. “It has the lower-respiratory severity of SARS and MERS coronaviruses, and the transmissibility of cold coronaviruses.”

One reason that SARS-CoV-2 may be so versatile, and therefore so successful, has to do with its particular talent for binding and fusing with lung cells. All coronaviruses use their spike proteins to gain entry to human cells, through a complex, multistep process. First, if one imagines the spike’s mushroom shape, the cap acts like a molecular key, fitting into our cells’ locks. Scientists call these locks receptors. In SARS-CoV-2, the cap binds perfectly to a receptor called the ACE-2, which can be found in various parts of the human body, including the lungs and kidney cells. Coronaviruses attack the respiratory system because their ACE-2 receptors are so accessible to the outside world. “The virus just hops in,” Perlman told me, “whereas it’s not easy to get to the kidney.”

While the first SARS virus attached to the ACE-2 receptor, as well, SARS-CoV-2 binds to it ten times more efficiently, Kizzmekia Corbett, the scientific lead of the coronavirus program at the National Institutes of Health Vaccine Research Center, told me. “The binding is tighter, which could potentially mean that the beginning of the infection process is just more efficient.” SARS-CoV-2 also seems to have a unique ability, which SARS and MERS did not have, to use enzymes from our human tissue—including one, widely available in our bodies, named furin—to sever the spike protein’s cap from its stem. Only then can the stem fuse the virus membrane and the human-cell membrane together, allowing the virus to spit its RNA into the cell. According to Lisa Gralinski, an assistant professor in the Department of Epidemiology at the University of North Carolina at

Chapel Hill, this supercharged ability to bind to the ACE-2 receptor, and to use human enzymes to activate fusion, “could aid a lot in the transmissibility of this new virus and in seeding infections at a higher level.”

Once a coronavirus enters a person—lodging itself in the upper respiratory system and hijacking the cell’s hardware—it rapidly replicates. When most RNA viruses replicate themselves in a host, the process is quick and dirty, as they have no proofreading mechanism. This can lead to frequent and random mutations. “But the vast majority of those mutations just kill the virus immediately,” Andersen told me. Unlike other RNA viruses, however, coronaviruses do have some capacity to check for errors when they replicate. “They have an enzyme that actually corrects mistakes,” Denison told me.

It was Denison’s lab at Vanderbilt that first confirmed, in experiments on live viruses, the existence of this enzyme, which makes coronaviruses, in a sense, cunning mutators. The viruses can remain stable in a host when there is no selective pressure to change, but rapidly evolve when necessary. Each time they leap into a new species, for example, they are able to hastily transform in order to survive in the new environment, with its new physiology and a new immune system to battle. Once the virus is spreading easily within a species, though, its attitude is, “I’m happy, I’m good, no need to change,” Denison said. That seems to be playing out now in humans; as SARS-CoV-2 circles the globe, there are slight variations among its strains, but none of them seem to affect the virus’s behavior. “This is not a virus that is rapidly adapting. It’s like the best car in the Indy 500. It’s out in front and there is no obstacle in its path. So there is no benefit to changing that car.”

{animation}

Caption: The coronavirus binds to host cells and fuses with the cell’s membrane, releasing its viral genome and hijacking the cell’s machinery to duplicate its RNA and create new viral proteins. The RNA and proteins are packaged into new virus particles, which are excreted from the cell to infect more cells.

A virus replicates in order to shed from its host—through mucus, snot, phlegm, and even our breath—as soon as possible, in great quantities, so that it can keep spreading. The coronavirus happens to be a

brilliant shedder. A preprint study by German researchers, published earlier this month, and one of the first outside China to examine data from patients diagnosed with COVID-19, found clear evidence that infected people shed the coronavirus at significant rates before they develop symptoms. In effect—possibly due to that supercharged ability to bind and fuse to our cells—the virus wears an invisibility cloak. Scientists recently estimated that undocumented cases of COVID-19, or infected people with mild symptoms, are fifty-five per cent as contagious as severe cases. Another study found that in more severe cases (requiring hospitalization), patients shed the virus from their respiratory tracts for as long as thirty-seven days.

Outside a host, in parasitical purgatory, a virus is inert, not quite alive, but not dead, either. A hundred million coronavirus particles could fit on the head of a pin—typically, thousands or tens of thousands are necessary to infect an animal or a person—and they might remain viable for long stretches. Researchers at the Virus Ecology Unit of Rocky Mountain Laboratories, in Montana, a facility connected to the National Institute of Allergy and Infectious Diseases, have found that the virus can linger on copper for four hours, on a piece of cardboard for twenty-four hours, and on plastic or stainless steel for as long as three days. They also found that the virus can survive, for three hours, floating through the air, transmitted by the tiny respiratory droplets an infected person exhales, sneezes, or coughs out. (Other research suggests the virus might be able to exist as an aerosol, but only in very limited conditions.) Most virus particles, though, seem to lose their virulency fairly quickly. The infection window is highest in the first ten minutes. Still, the risk of infection has turned many of us, understandably, into germophobes.

The coronavirus enters the body through the mouth, eyes, and nose, then makes its way to the lungs, where particles replicate. It is primarily transmitted to others through coughing and sneezing.

All a virus wants is an endless chain of hosts. Contagion is the evolutionary end goal. Based on experiments so far, researchers estimate that COVID-19 is slightly more communicable than the common flu and less communicable than the most highly infectious viruses, like measles, with which a single sick person can infect around twelve other people.

There are likely coronavirus super-spreaders—people who, for whatever reason, are almost entirely asymptomatic but transmit the disease to many other people. But pinning down an exact infection rate, at this point, is an impossible task. “We tend to focus on these absolute numbers as telling us how worried we should be,” Denison said. “Look, it’s like flooding. You know, is it up to my knees or is it up to my chin? It doesn’t matter. I need to do something to try to make sure I’m not gonna drive my car into the flood.”

In many places, we already have driven into the flood. As hundreds of people die each day, hospitals are running out of supplies, beds, and ventilators. In these severe COVID-19 cases, according to scientists’ current understanding, the disease may have more to do with a haywire immune response to the virus than anything else. Because the virus can gain a foothold in our lower respiratory system while still wearing that invisibility cloak, it “basically beats the immune system to the punch and starts replicating too rapidly,” Perlman said. When the immune system finally does register its presence, it might go into overdrive, and send everything in its arsenal to attack, since it has no specific antibodies to fight these strange new invaders. “It’s like pouring gas on the fire,” Denison told me. The lung tissue swells and fills with fluid. Breathing is restricted, as is the exchange of oxygen. “The host immune response just gets triggered to such an extreme level, and then builds on itself and builds on itself until ultimately the body kind of goes into shock,” Gralinski said. It is almost like an autoimmune disease; the immune system is attacking parts of the body that it should not.

This type of response might be why the elderly are, on the whole, more vulnerable to COVID-19, just as they were to the SARS outbreak in 2003. (In that outbreak, there were almost no deaths among children under the age of thirteen, and, when kids did get sick, the disease was, on average, milder than what affected adults.) When studying SARS in mice models, Denison told me that he has observed a phenomenon known as “immune senescence,” in which older mice no longer had the capacity to respond in a balanced way to a new virus; their immune systems’ overreaction then caused even more severe disease. This occurred in some of the worst cases during the first SARS outbreak, too, Denison said, and explains why antiviral drugs may be significantly more helpful

at the onset of illness, before the immune system has had a chance to wreak havoc.

In the last decade, Denison’s lab and collaborators at the University of North Carolina have been researching antiviral treatments to try to find something that worked not just against SARS and MERS but for a new coronavirus which, they knew, would inevitably arrive. Together, they did much of the early research into the drug now known as Remdesivir, which is currently in development by Gilead and in studies on infected patients, and another antiviral drug compound, known as NHC. Both drugs, in animal models, were able to bypass, avoid, or block the coronavirus’s proofreading function {reverse transcriptase?}, which helped stop the virus from replicating successfully in the body. “They worked very effectively against all the coronaviruses that we’ve tested,” Denison told me.

Coronaviruses likely have that proofreading enzyme because they are huge—one of the largest RNA viruses in existence—and they need a mechanism that maintains such a long genome’s structure. From our perspective, the benefit of such a big genome, Andersen told me, “is that the more genes and protein products a virus has, the more opportunities we have to design specific treatments against them.” For instance, the virus’s unique ability to use the human enzyme furin offers promise for antiviral drugs that act as furin inhibitors.

COVID-19, while still new to us hosts, will continue to be responsible for widespread infection and death. But, Epstein said, “Over time, as viruses evolve with their natural habitats, they tend to cause less severe disease. And that is good for both the host and the virus.” The more virulent strains might burn out (which, however, means many more awful deaths), while the remaining hosts might build up some immunity. More immediately, and urgently, the virus’s stability—how much it is thriving among us right now, and mutating only minimally—bodes well for the performance of antiviral drugs and, eventually, a vaccine. If the growing number of mitigation measures—this unprecedented national and international shutdown—are held in place for enough time, the speed at which the virus is spreading should slow, giving hospitals and health workers some relief. “The virus is our teacher,” Denison told me. It has

spent thousands of years evolving to get where it is.
We're now just rushing to catch up.

Link

<https://www.newyorker.com/science/elements/from-bats-to-human-lungs-the-evolution-of-a-coronavirus>