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What the Future May Hold for the Coronavirus and Us

By Emily Anthes October 12, 2021

On Jan. 9, 2020, about a week after the world first learned of a mysterious cluster of pneumonia cases in central China, authorities announced that scientists had found the culprit: a novel coronavirus.

It was a sobering announcement, and an unnervingly familiar one. Nearly two decades earlier, a different coronavirus had hurdled over the species barrier and sped around the world, causing a lethal new disease called severe acute respiratory syndrome, or SARS. The virus, which became known as SARS-CoV, killed 774 people before health officials contained it.

But even as scientists worried that history might be repeating itself, there was one glimmer of hope. Although all viruses evolve, coronaviruses are known to be relatively stable, changing more slowly than the common flu.

> "There was, I think, a sense that would work in our favor, and that the nightmare scenario of it being like influenza – constantly changing and needing updated vaccines all the time – would probably not be the case," said Dr. Adam Lauring, a virologist and infectious disease physician at the University of Michigan.

What many scientists had not counted on was unchecked global spread. Over the following weeks, the new virus, SARS-CoV-2, skipped from Wuhan, China, to a cruise ship in Japan, a small town in northern Italy and a biotechnology conference in Boston. Country by country, global coronavirus trackers turned red.

To date, more than 237 million people have been infected with the virus, and 4.8 million have died – 700,000 in the United States alone.

With every infection come new opportunities for the virus to mutate. Now, nearly two years into the pandemic, we are working our way through an alphabet of new viral variants: fast-spreading Alpha, immune-evading Beta, and on through Gamma, Delta, Lambda and, most recently, Mu.

"We just have uncontrolled infections in much of the world, and that's going to lead to more chances for the virus to evolve," Dr. Lauring said.

> Even for a virus, evolution is a long game, and our relationship with SARS-CoV-2 is still in its infancy. We are extremely unlikely to eradicate the virus, scientists say, and what the next few years – and decades – hold is difficult to predict.

But the legacy of past epidemics, as well as some basic biological principles, provides clues to where we could be headed.

Past Pandemics Remind Us Covid Will Be an Era, Not a Crisis That Fades

History repeatedly demonstrates how difficult it is to decisively declare that a pandemic is over.

The genetic lottery

Viruses are replication machines, hijacking our cells to make copies of their own genomes. Sometimes they make small mistakes, akin to typos, as they replicate.

Most of the time, these errors have no benefit for the virus; many are harmful and quickly disappear. But occasionally, a virus hits the genetic lottery: a mutation that confers an advantage. This fitter version of the virus can then outcompete its peers, giving rise to a new variant.

The coronavirus could shift in countless ways, but there are three concerning possibilities: It could become more transmissible, it could become better at evading our immune system or it could become more virulent, causing more serious disease.

SARS-CoV-2 has already become more transmissible. "The virus is just better at transmitting from one person to another than it was in January of 2020," said Jesse Bloom, an expert in viral evolution at the Fred Hutchinson Cancer Research Center in Seattle. "And this is due to a variety of mutations that the virus has acquired, some of which we understand and some of which we don't."

> One of the first of these mutations had already emerged by late January 2020. The mutation, D614G, likely stabilized the spike protein that the virus uses to latch onto human cells, making the virus more infectious. It quickly became widespread, displacing the original version of the virus.

As the virus spread, more mutations sprang up, giving rise to even more transmissible variants. First came Alpha, which was about 50% more infectious than the original virus, and soon Delta, which was, in turn, roughly 50% more infectious than Alpha.

"Now we're basically in a Delta pandemic," said Robert Garry, a virologist at Tulane University. "So another surge, another spread of a slightly better variant."

Although some experts were surprised to see the hyperinfectious variant, which has more than a dozen notable mutations, emerge so quickly, the appearance of more transmissible variants is textbook viral evolution.

"It's hard to imagine that the virus is going to pop into a new species perfectly formed for that species," said Andrew Read, an evolutionary microbiologist at Penn State University. "It's bound to do some adaptation."

But scientists don't expect this process to continue forever.

There are likely to be some basic biological limits on just how infectious a particular virus can become, based on its intrinsic properties. Viruses that are well adapted to humans, such as measles and the seasonal influenza, are not constantly becoming more infectious, Dr. Bloom noted.

It is not entirely clear what the constraints on transmissibility are, he added, but at the very least, the new coronavirus cannot replicate infinitely fast or travel infinitely far.

> "Transmission requires one person to somehow exhale or cough or breathe out the virus, and it to land in someone else's airway and infect them," Dr. Bloom said. "There are just limits to that process. It's never going to be the case that I'm sitting here in my office, and I'm giving it to someone on the other side of Seattle, right?"
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> He added: "Whether the Delta variant is already at that plateau, or whether there's going to be further increases before it gets to that plateau, I can't say. But I do think that plateau exists."

Dodging immunity

In addition to becoming more transmissible, some variants have also acquired the ability to dodge some of our antibodies. Antibodies, which can prevent the virus from entering our cells, are engineered to latch onto specific molecules on the surface of the virus, snapping into place like puzzle pieces. But genetic mutations in the virus can change the shape of those binding sites.

"If you change that shape, you can make it impossible for an antibody to do its job," said Marion Pepper, an immunologist at the University of Washington School of Medicine.

Delta appears to evade some antibodies, but there are other variants, particularly Beta, that are even better at dodging these defenses. For now, Delta is so infectious that it has managed to outcompete, and thus limit the spread of, these stealthier variants.

But as more people acquire antibodies against the virus, mutations that allow the virus to slip past these antibodies will become even more advantageous. "The landscape of selection has changed," said Jessica Metcalf, an evolutionary biologist at Princeton University. "From the point of view of the virus, it's no longer, 'I just bop around, and there's a free host.'"

> The good news is that there are many different kinds of antibodies, and a variant with a few new mutations is unlikely to escape them all, experts said.

"The immune system has also evolved to have plenty of tricks up its sleeve to counteract the evolution of the virus," Dr. Pepper said. "Knowing that there is this complex level of diversity in the immune system allows me to sleep better at night."

Certain T cells, for instance, destroy virus-infected cells, helping to reduce the severity of disease. Together, our assortment of T cells can recognize at least 30 to 40 different pieces of SARS-CoV-2, researchers have found.

"It's a lot harder to evade T cell responses than antibody responses," said Dr. Celine Gounder an infectious disease specialist at the New York University Grossman School of Medicine.

And then there are B cells, which generate our army of antibodies. Even after we clear the infection, the body keeps churning out B cells for a while, deliberately introducing small genetic mutations. The result is an enormously diverse collection of B cells producing an array of antibodies, some of which might be a good match for the next variant that comes along.

"They're actually a library of guesses that the immune system makes about what variants might look like in the future," said Shane Crotty, a virologist at the La Jolla Institute for Immunology.

So far, studies suggest that our antibody, T cell and B cell responses are all working as expected when it comes to SARS-CoV-2. "This virus is mostly playing by immunological rules we understand," Dr. Crotty said.

'No interest in killing us'

> Whether the virus will become more virulent – that is, whether it will cause more serious disease – is the hardest to predict, scientists said. Unlike transmissibility or immune evasion, virulence has no inherent evolutionary advantage.

"The virus has no interest in killing us," Dr. Metcalf said. "Virulence only matters for the virus if it works for transmission."

Because people who are hospitalized may be less likely to spread the virus than those who are walking around with the sniffles, some have theorized that new viruses become milder over time.

One commonly cited example is the myxoma virus, which Australian scientists released in 1950 in an attempt to reduce the population of invasive European rabbits.

Initially, the myxoma virus proved to be "fantastically virulent," one scientist wrote, killing more than 99% of the rabbits it infected. After just a few years, however, several somewhat milder strains of the virus emerged and became dominant.

But myxoma is not a simple story of a virus gradually becoming less virulent.

"Early variants that were too nice were also discovered in the mid-1950s," said Dr. Read, who has studied the virus. "They caused little disease but transmitted poorly, so never came to dominate."

The rabbits also evolved new immune defenses that allowed them to fight off infection more easily, and then the virus fired back, acquiring new tricks for depressing the rabbits' immune systems.

"Seventy years – it's still going gangbusters," Dr. Read said.

> It is too early to say whether SARS-CoV-2 will change in virulence over the long-term. There could certainly be trade-offs between virulence and transmission; variants that make people too sick too quickly may not spread very far.

Then again, this virus spreads before people become severely ill. As long as that remains true, the virus could become more virulent without sacrificing transmissibility.

Moreover, the same thing that makes the virus more infectious – faster replication or tighter binding to our cells – could also make it more virulent. Indeed, some evidence suggests that Delta is more likely to result in hospitalization than other variants.

"I could actually keep this game of imagining going on for a long time," Dr. Read said. "On my good days, I'm optimistic that the disease severity will go down through time. Because clearly, people being isolated does affect transmission. On my bad days, I worry about it going the other direction."

Uneasy equilibrium

Although many possible paths remain open to us, what is certain is that SARS-CoV-2 will not stop evolving – and that the arms race between the virus and us is just beginning.

We lost the first few rounds, by allowing the virus to spread unchecked, but we still have powerful weapons to bring to the fight. The most notable are highly effective vaccines, developed at record speed. "I think there is hope in the fact that the SARS-CoV-2 vaccines at this point are more effective than flu vaccines have probably ever been," Dr. Bloom said.

Even the first generation vaccines provide substantial protection against disease, and there is plenty of room to improve them by tinkering with the dosing and timing, tailoring them to new variants or developing new approaches, such as nasal sprays that may be better at halting transmission.

> "I have great faith that we can sort any detrimental evolutionary trajectories out by improving our current or next generation vaccines," Dr. Read said.

The occasional breakthrough infection or booster could help top up our flagging immunity and teach our bodies to recognize new mutations, ultimately making us less vulnerable to the next variant that comes along.

"Maybe you have a re-infection, but it's relatively mild, which also boosts your immunity," Dr. Gounder said.

Meanwhile, as the number of completely vulnerable hosts dwindles, and transmission slows, the virus will have fewer opportunities to mutate. One recent paper, which has not yet been reviewed by experts, suggests that rising vaccination rates may already be suppressing new mutations.

And the evolution rate could also slow down as the virus becomes better adapted to humans.

"There's low-hanging fruit," Dr. Lauring said. "So there are certain ways it can evolve and make big improvements, but after a while there aren't areas to improve – it's figured out all the easy ways to improve."

Eventually, as viral evolution slows down and our immune systems catch up, we will reach an uneasy equilibrium with the virus, scientists predict. We will never extinguish it, but it will smolder rather than rage.

What that equilibrium point looks like exactly – how much transmission there is and how much disease it causes – is uncertain. Some scientists predict that the virus will ultimately be much like the flu, which can still cause serious illness and death, especially during seasonal surges.

> Others are more optimistic. "My guess is that one day this is going to be another cause of the common cold," said Jennie Lavine, who explored that possibility as an infectious disease researcher at Emory University.

There are four other coronaviruses that have become endemic in human populations. We are exposed to them early and often, and all four mostly cause run-of-the-mill colds.

Covid-19 might just be what it looks like when a novel coronavirus spreads through a population without any pre-existing immunity. "This may not be such a different beast than everything else that we're accustomed to," Dr. Lavine said. "It's just a bad moment."

Of course, plenty of uncertainties remain, scientists said, including how long it will take to reach equilibrium. With infections beginning to decline again in the United States, hopes are again rising that the worst of the pandemic is behind us.

But much of the world remains unvaccinated, and this virus has already proved capable of surprising us. "We should be somewhat cautious and humble about trying to predict what it is capable of doing in the future," Dr. Crotty said.

While we can't guard against every eventuality, we can tip the odds in our favor by expanding viral surveillance, speeding up global vaccine distribution and tamping down transmission until more people can be vaccinated, scientists said.

The actions we take now will help determine what the coming years look like, said Dr. Jonathan Quick, a global health expert at Duke University and the author of "The End of Epidemics."

> The future, he said, "depends much, much more on what humans do than on what the virus does."