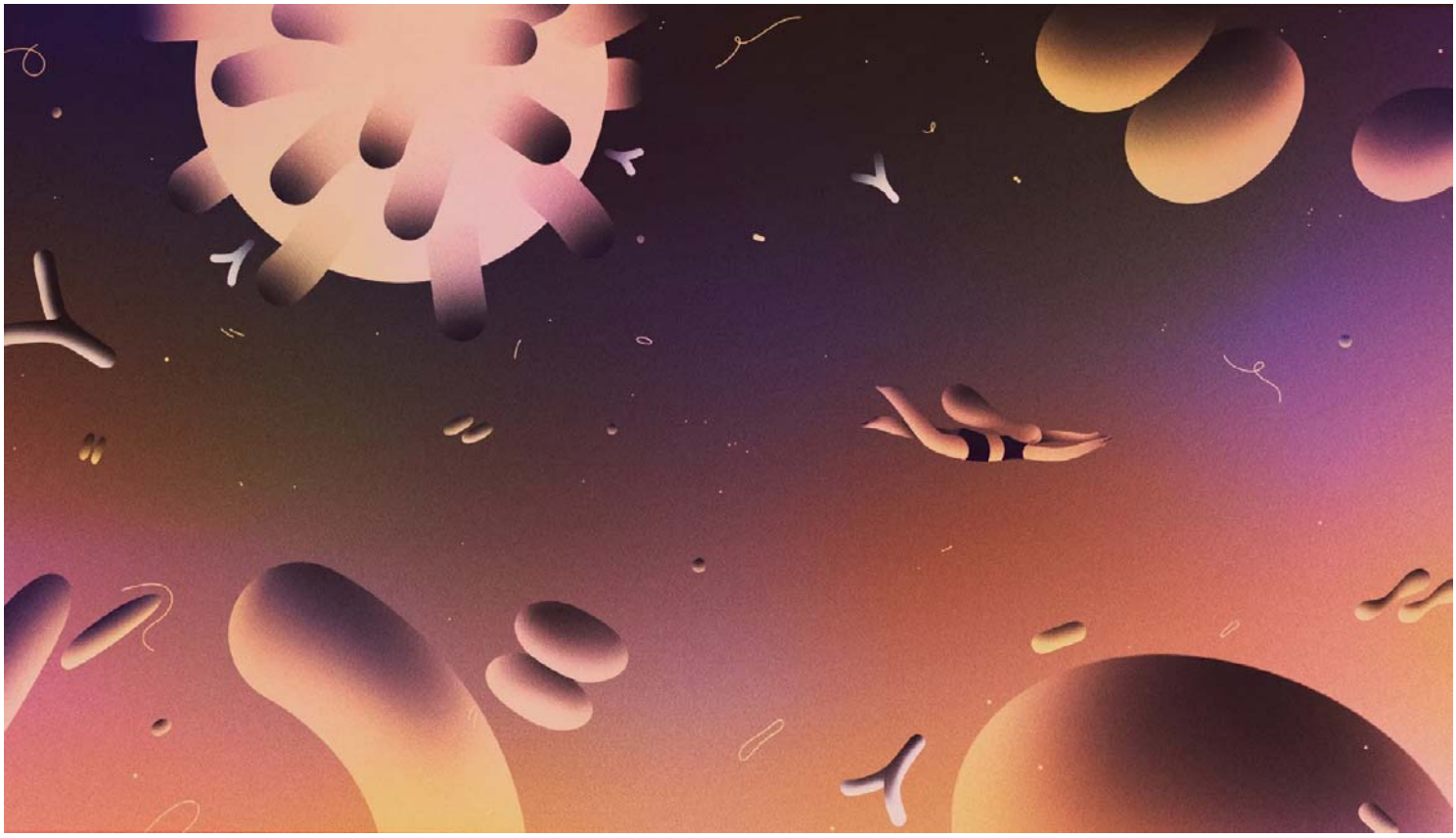

Illustration by Sophi Miyoko Gullbrants

ANNALS OF MEDICINE

COEXISTING WITH THE CORONAVIRUS

COVID-19 is likely to become an endemic disease. How will our immune systems resist it?

By Katherine S. Xue

July 21, 2021

In the spring of 1846, a Dutch physician named Peter Ludwig Panum arrived on the Faroe Islands, a volcanic chain about two hundred miles northwest of Scotland. He found the Faroes to be a harsh and unforgiving place. The islands' eight thousand inhabitants, who were Danish subjects at that time, spent their days outdoors, buffeted by sea winds, fishing and tending sheep. The conditions, Panum wrote, were unlikely "to prolong the lives of the inhabitants." And yet, despite the scarcity of medical care and a diet of wind-dried, sometimes rancid meat, the average Faroese life span was forty-five years, which matched or exceeded that in mainland Denmark. The islanders benefitted from a near-complete lack of infectious disease; many illnesses, including smallpox and scarlet fever, rarely reached them. Panum had arrived to study a measles epidemic—the first outbreak of that virus in the Faroe Islands in sixty-five years.

For the most part, the course of the outbreak was devastating and predictable. In six months' time, more than three-quarters of the islands' inhabitants were infected, and about a hundred people died. But the outbreak was also unusual in many ways. In mainland Europe, measles was typically a childhood infection. Few Faroese children died in the outbreak; instead, adults bore the brunt. Their mortality rates increased with every decade of life until about the age of sixty-five, and then dropped off. It turned out that those who'd been infected during the islands' last measles epidemic, in 1781, were still protected by the immunity that they'd acquired decades before. Of these "aged people," Panum wrote, "not one, as far as I could find out by careful inquiry, was attacked the second time."

Read *The New Yorker's* complete news coverage and analysis of the coronavirus pandemic.

Panum's study remains a striking demonstration of a remarkable fact: the body remembers. It learns to recognize the pathogens it encounters, and, in some cases, it can hold on to those memories for decades, even a lifetime. Ancient civilizations knew about immune memory long before they understood it; Thucydides, in his account of the plague of Athens, wrote that "the same man was never attacked twice—never at least fatally." Many of us draw our ideas about the immune system from stories like these. We think of immunity as a binary state: without it, we're vulnerable; with it, we're safe.

For many pathogens, however, including coronaviruses, immunity is less clear-cut. The coronavirus family includes SARS-CoV-2, the virus responsible for COVID-19, along with four seasonal coronaviruses—HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63—which together cause an estimated ten to thirty per cent of common colds. Today, these seasonal coronaviruses are the cause of common childhood infections, as measles was in Panum's time. In sharp contrast to measles, though, adults are reinfected by seasonal coronaviruses every few years.

Much of what we know about these reinfections comes from the Common Cold Unit, a remarkable British research program whose studies of virus transmission and treatment involved more than eighteen thousand human volunteers over the course of forty-four years. In one of the unit's last studies, published in 1990, fourteen healthy volunteers were exposed to seasonal coronavirus 229E by means of a nasal wash. They returned, a year later, to receive a second, identical dose. Of the nine people who were successfully infected the first time, six were infected again in the second exposure. The five volunteers who'd escaped the virus the first time were all infected, too. The fact of the reinfections might seem alarming, but the volunteers who'd been reinfected had fewer symptoms and were less likely to transmit the virus to others. They weren't completely immune, but they retained a degree of immunity—low enough to allow for reinfection, but high enough to render the virus less potent.

This murky portrait of coronavirus immunity will shape our future as the U.S. brings COVID-19 under control. After getting the virus, the vaccine, or both, at least a hundred and sixty million Americans have acquired some form of immunity. Still, it is likely that the virus itself is here to stay. "I personally think that there's essentially zero chance that SARS-CoV-2 will be eradicated," Jesse Bloom, a virologist at the Fred Hutchinson Cancer Research Center, told me. (Bloom advised my Ph.D. research on influenza evolution.) Most viruses, including the four seasonal coronaviruses, other common-cold viruses, and the flu, haven't been eradicated; scientists describe them as "endemic," a term derived from the Greek word *éndēmos*, meaning "in the people." Endemic viruses circulate constantly, typically at low levels, but with occasional, more severe outbreaks. We don't shut out these endemic viruses with quarantines and stay-at-home orders; we live with them.

What will it be like to live with endemic SARS-CoV-2? That depends on the strength of our immune memories. How vividly will our bodies remember the virus or vaccine? How will waning immunity and the rise of variants—such as Delta, which is currently driving a spike in COVID cases around the world—affect our vulnerability to reinfection? We're beginning to learn the answers to some of these questions, and to get a sense of the years to come.

On May 13, 2020, a fishing vessel left Seattle in search of hake. Before boarding, the ship's hundred and twenty-two crew members were tested for the coronavirus, and also for antibodies against it, which indicate prior infection. Three crew members tested positive for antibodies before departure; everyone tested negative for the virus. But, while at sea, a member of the crew fell ill and tested positive. A ship at sea is an island, and the coronavirus spread rapidly. When the vessel returned to shore, after an eighteen-day voyage, a hundred and three crew members tested positive for the coronavirus. And yet none of the three crew members who'd possessed antibodies before boarding were infected a second time. In October, 2020, when these results were reported in the *Journal of Clinical Microbiology*, it wasn't yet clear whether antibodies that formed during an initial infection could protect against reinfection. The vessel had brought home reassuring news.

Antibodies aren't always the first line in our immune defense. When our cells encounter a new virus, they first respond by means of the so-called "innate" immune system, which shuts down many incipient infections quickly, before they grow out of control. This initial response is nonspecific; for the most part, it's the same for every pathogen, novel or familiar. It's only a few days later that the "adaptive" immune system—the home of immune memory—shifts into gear. Part of that ramping up involves B cells, which make antibodies. As a matter of course, our bodies produce millions of B cells, each tuned, in a more or less random way, to make a different kind of antibody; these antibodies are so diverse that one will inevitably match whatever pathogen might infect us. During an infection, the B cells that happen to be well suited to the new invader receive a signal to multiply. The antibodies they produce circulate in the bloodstream, binding to virus particles and disabling them.

The fishing-vessel study confirmed that the antibody response inspired by an initial SARS-CoV-2 exposure could protect against subsequent infections for some period of time. Immune memory had taken root. "Those B cells will, in many cases, persist through the rest of your life and keep cranking out antibodies, so your body will now remember whatever you've been exposed to," Bloom, who was one of the authors of the study, said. And yet there are degrees of immune memory. Antibodies against certain viruses, such as measles, mumps, rubella, and smallpox, persist at extraordinarily stable levels for many decades; it's because of that persistence that the "aged people" in Panum's study were able to resist disease a lifetime later. But not all antibody responses are so durable. In 2007, researchers published a study of workers at the Oregon National Primate Research Center. The workers' blood is tested regularly for exposure to animal diseases. The researchers found that, although some antibody levels stayed high, others fell over time. Antibodies against tetanus and diphtheria, two bacterial toxins, fell to half their previous levels in ten to twenty years.

The gradual erosion of antibody levels in the blood can lower protection and render us vulnerable to reinfection. An important unanswered question about SARS-CoV-2, therefore, is how long our antibody responses will last. "Long term, do your antibodies go to a stable plateau that persists for the rest of your life, or is it a downward-sloping line?" Bloom asked. For SARS-CoV-2, specifically, it's too early to know. But long-term studies of its relatives, the viruses that cause SARS and MERS, have found that antibody levels can decline detectably in the two or three years after an infection. Time may erode levels of COVID antibodies as well.

Decline is not disappearance. Even if antibody levels go down from their initial post-infection peak, they may remain high enough to prevent a viral exposure from becoming an infection, or to keep an infection from progressing into severe disease. Onboard the fishing vessel, two of the three protected crew members had only modest antibody levels. The virus still left them untouched.

Immune memory isn't inscribed in antibodies alone. "There is a whole array of memory cells that are just waiting to get reactivated," Marion Pepper, an immunologist at the University of Washington, told me. In addition to the B cells that make antibodies, we possess T cells—marauding defenders capable of destroying the body's own cells if they've been infected with a virus. Like antibodies, T cells come to circulate at lower levels over time. But both adaptive systems boot up faster upon reinfection. "It takes five to seven days to mount an adaptive immune response when you first see a virus," Pepper said. "But it can take as little as two to four hours when you see it again."

Last summer, Pepper's lab conducted a detailed study of immunity in fifteen volunteers who'd had mild COVID-19 infections three months earlier. The researchers looked for antibodies, but also for so-called "memory" B and T cells—scouts that live in our tissue and bloodstream, monitoring for the reappearance of specific pathogens from the past. When these memory cells recognize an old foe, they sound the alarm, speeding the multiplication of pathogen-specific B and T cells. Memory cells are "little needles in a haystack," Pepper told me, but the researchers still found ones tuned to the coronavirus, even though their research subjects had experienced only mild symptoms. "I have a lot of faith in the immune system," Pepper said.

The immune system's overlapping layers work together to strengthen its memory. But viruses aren't static. As they accumulate mutations, their shapes shift, and they gradually become more difficult for the system to recognize. Survivors of the 1918 flu pandemic maintained strong antibody responses against that virus for almost ninety years. And yet adults still get the flu approximately once every five years, because the influenza virus's rapid evolution insures that each year brings new variants. On average, flu viruses acquire half a dozen mutations each year; many of these alter the proteins that allow the viruses to enter and exit host cells. Antibodies that once bound tightly to a virus may have a weaker grip on its evolved form; the virus might escape the notice of certain T cells that used to recognize it.

"You can also ask the question for coronaviruses," Bloom said. "How much of the ability to reinfect people might be driven by the virus changing?" Growing evidence suggests how much viral evolution might make us vulnerable to coronavirus reinfection. Recently, researchers in Bloom's lab analyzed blood samples collected from people in the nineteen-eighties and nineties; the samples contained antibodies for the version of seasonal coronavirus 229E that circulated back then. Those same antibodies failed to recognize the descendants of the virus that had evolved in the intervening years. Coronaviruses mutate more slowly than viruses like influenza and H.I.V., but, over the course of a decade or two, they can still change enough to evade our immune memory.

Today, we are grappling with several coronavirus variants that are more transmissible—and possibly more deadly—than the original strain of SARS-CoV-2. Antibodies created in response to the initial virus or the current vaccines bind more poorly to several of these variants, creating opportunities for reinfection. The city of Manaus, in the Brazilian Amazon, is a case that has given researchers some reason for concern. In early 2020, the coronavirus spread there virtually unchecked; by October, tests showed that about half of the city's inhabitants harbored antibodies, leading some scientists to declare that the area had reached herd immunity. But, in December, the city experienced a second coronavirus surge that was even more severe than the first, causing more hospitalizations and deaths than the initial wave.

The causes of this second wave have been the subject of worried speculation, and, as with so much of the pandemic, there's no single explanation. Some of the blame lies with the relaxation of social-distancing guidelines during the holiday season in a city that believed itself immune. The initial study that calculated high antibody prevalence may also have overestimated prior infection in the broader population. But a variant called P.1, or Gamma, which was first detected in Manaus in early December, also bears at least some responsibility. Early evidence has shown that antibodies created in response to the original coronavirus seem to provide less protection against the Gamma variant; in a preprint of a study that has not yet been peer-reviewed, scientists estimated that, by the end of the second wave, as many as one in six infections with Gamma were reinfections. By February, the variant was responsible for nearly all of the city's cases; it has since spread rapidly through Brazil and now accounts for almost one in sixteen infections in the U.S.

Variants like Gamma rightly concern us, and in the past few weeks the more contagious Delta variant has driven outbreaks in regions of the U.S. with low vaccination rates. But with these variants, too, immunity is gradual, not binary. The variants are, for the most part, still quite similar to the original virus. Many of the defenses created by vaccination or an initial exposure remain in place even as the virus begins to change. "Seldom does a mutation totally destroy the ability of antibodies to recognize a virus," Scott Hensley, an immunologist at the University of Pennsylvania, told me. So far, studies indicate that the Pfizer, Moderna, and Johnson & Johnson vaccines protect against the coronavirus variants of concern, even though the antibodies elicited by the vaccines are slightly less effective at recognizing the virus's evolved forms. A mutation could affect the binding of some antibodies, even as others continue to do their job. T-cell immunity is even more durable: whereas antibodies bind to the surfaces of viral proteins, T cells recognize short pieces of those proteins that have been chewed up and presented by cells; these pieces, which often come from the insides of a virus, tend to stay the same even when the more malleable surface of the virus evolves. "There's a lot of redundancy in this system," Pepper said. Even if variants manage to weave their way around some of our immune defenses, they can still get tripped up by others. Meanwhile, clinical trials for boosters and updated vaccines are already under way.

It's possible, over the long term, for our immune memories to begin working against us. For decades, flu researchers have observed that adults deploy their strongest antibody responses against flu strains that they encountered in childhood. In this phenomenon, which scientists call "original antigenic sin," immune memories from childhood cast a long shadow into our adult lives. Antibodies formed during an initial viral encounter continue to respond to infections and vaccinations that take place decades later—even after a virus has evolved—making the immune system less effective at updating its response. "You wake up immune memory against antigens that are no longer there," Hensley said. These ineffective antibodies can prevent the immune system from updating its response; the system insists on fighting the last war. In the far-off future, original antigenic sin may shape our bodies' responses to SARS-CoV-2, making it harder to hone our immune defenses against new strains. It's a poignant and sobering idea: sometimes we remember so well that the memory itself becomes a blind spot.

For now, though, it's the pace of global vaccination that will most powerfully determine our near-term future with COVID. "The single best thing we can do is to vaccinate the world as fast as possible to limit viral evolution," Alex Greninger, a virologist at the University of Washington, told me. (As a researcher, I have collaborated with both Hensley and Greninger.) More infections give the virus more opportunities to evolve, and, as the past year has shown, variants can spread quickly around the globe no matter where they arise. The pandemic won't be truly over until it's over for everyone.

Immunitas, the Latin word from which "immunity" derives, is a legal term used to describe exemption from taxation or jurisdiction. But the epidemiological world is messier than the legal one. Another term may better convey its complexities:

"resistance," which comes from the Latin verb *resistere*, meaning "to hold back." Immune resistance holds back the virus. It makes viral exposure less likely to turn into an infection—asymptomatic or otherwise—or into severe disease. Vaccinations and infections, especially longer infections, tend to build up our resistance to pathogens. Time and viral mutation gradually wear it down. The higher our immune resistance, the more viral exposure we can tolerate without getting sick. The lower our resistance, the more likely we are to experience disease.

This graduated view of immunity is important for understanding coronavirus reinfections. The world's first confirmed COVID reinfection was detected last August, when a thirty-three-year-old man flew from Spain to Hong Kong and tested positive for the virus upon arrival. The man had experienced a mild infection almost five months earlier; he'd had symptoms for only a few days, and, for whatever reason, had developed no detectable antibodies after that initial infection. And yet his second bout was entirely asymptomatic, and the virus became undetectable within a week. "This is a textbook example of how immunity should work," the Yale immunologist Akiko Iwasaki wrote, on Twitter. "While immunity was not enough to block reinfection, it protected the person from disease." Perhaps the man's initial antibody response had been too weak to stop the virus from taking hold, but other layers of immunity kept the infection under control. Meanwhile, five days into his second infection, the patient tested positive for COVID antibodies, suggesting that the reëxposure had boosted his immune response.

Recently, large-scale studies have begun to quantify the frequency of coronavirus reinfection. As the fishing-vessel analysis suggested, rates of reinfection appear to be low. Studies in Denmark and the U.K. have found that, several months after testing positive for COVID-19, adults are eighty per cent less likely to get infected by the virus. When reinfections do occur, they are likely to be mild or entirely asymptomatic. Even if the virus gains a foothold in the body, resistance can limit its effects.

The same perspective applies to so-called vaccine breakthroughs—infections that occur in fully vaccinated individuals. Though breakthrough infections undoubtedly occur, these cases, like reinfections, are much more likely to be mild or asymptomatic. A hundred million U.S. adults were fully vaccinated in the first four months of this year; among them, the C.D.C. documented about ten thousand breakthrough infections by the end of April. Only a thousand of those resulted in hospitalization; that is, only one in a hundred thousand vaccinated individuals were hospitalized with COVID during that period. So far, it does not appear that these breakthrough infections are disproportionately caused by variants of concern. About a quarter of the reported breakthroughs were asymptomatic; in all likelihood, this is a vast underestimate, since many vaccinated individuals may never have realized that they were reinfected in the first place.

Today, reports of reinfections and vaccine breakthroughs tend to come as a scary surprise. But they will increasingly feel normal as the acute phase of the pandemic draws to a close. Despite the spectacular success of the vaccines, the odds are stacked against eradication or even herd immunity; the virus is too widespread and transmissible for that. Still, our relationship with the virus is going to change fundamentally. A year and a half ago, we were islanders blindsided by a new invader. As our collective immune resistance grows, however, COVID will shift from a pandemic to an endemic threat. The virus will continue to circulate at low levels, but its spread will be slower, and most infections will be less severe. It may primarily infect unvaccinated children—who often have asymptomatic infections and almost never develop severe symptoms—and cause occasional mild infections in vaccinated adults. Certain groups, such as the elderly and the immunocompromised, will still be at higher risk for severe complications; the vulnerable may die of COVID-19 the way they die of influenza and pneumonia today. But the risks will be lower for individuals who have some immune resistance. For most of us, COVID will become a familiar foe, like the flu—one of the background hazards of daily life.

This vision of an endemic-COVID future contains echoes of the past. Since the beginning of the twentieth century, there have been four influenza pandemics; each introduced a new version of the flu that continued to circulate for decades. (The 1968 and 2009 pandemics are responsible for the seasonal-flu strains that exist today.) Scientists speculate that common-cold viruses, too, could have their origins in past pandemics. Some indirect evidence suggests that the seasonal coronavirus OC43 may have originated in the pandemic of 1889, which killed a million people around the globe.

In a world with endemic COVID, you might catch the virus, or get vaccinated, as a kid, then get a booster with your flu shot every year. There will probably be COVID seasons, like flu seasons, in the winter; every few years, as new variants accumulate, a season might be especially bad. You will probably get COVID once every few years, too. Sometimes it will be mild, and you'll cough and feel tired for a day or two, as with any common cold; these brushes with the virus will strengthen your immune resistance. Sometimes an infection will be worse. Maybe you skipped your booster shot that year, or there's a new variant on the rise; maybe you were exposed to a lot of the virus when you spent time with a friend or co-worker who was sick. Whatever the reason, some infections may put you in bed for a week or more. As you get older, and your immune system weakens, the chance of complications will increase, as it does with the flu. If you grow more vulnerable, you might consider becoming more cautious about travelling or going out when a bad COVID season is in full swing—you might even wear a mask. (Perhaps the pandemic will have inspired you to wear one to avoid the flu, too.) The virus will stay with us, but widespread immune resistance will have dampened its worst effects.

The prospect of a long-term future with COVID might come as a disappointment. Smallpox, the only human virus ever eradicated, was successfully eliminated in 1980, after a lengthy vaccination campaign; the global eradication of polio is in its final stage. In the United States, childhood vaccinations have built up herd immunity against formerly common viruses like measles and mumps, limiting them to occasional outbreaks. We'd like the coronavirus to recede into historical memory, too. And yet immune memory doesn't always last, especially for a changing virus. Our bodies won't remember COVID perfectly, and so our minds won't be able to forget.

MORE ON THE CORONAVIRUS

- We have reached the beginning of the end of the American pandemic.
- But, without global vaccine equity, the virus will continue to evolve.
- What if we are too scared to return to normalcy?
- The sudden rise of the coronavirus lab-leak theory.
- How a city comes back to life.
- Sign up for our daily newsletter to receive the best stories from *The New Yorker*.

Katherine S. Xue is a postdoctoral fellow at Stanford University, where she studies microbiome evolution.