SCIENTIFIC AMERICAN
Health & Medicine

October–November 2020

9 Essential Facts about the Coronavirus Pandemic

WHAT WE KNOW SO FAR

WITH COVERAGE FROM nature

Plus:

U.S. PANDEMIC PREPAREDNESS FAIL

BLOOD TEST FOR CANCER

HOW TO COMBAT LONELINESS

LIZ TORMES

A Matter of Time

The past six months have felt like an eternity for those of us isolating and staying home. And I imagine they've also felt like a stressful slog to every essential worker who has showed up day in, day out, to keep people fed and healthy. But for science and medical research, six months is a relative blink of an eye. Scientific understanding about new diseases such as SARS-CoV-2 usually takes years, not months. Consider that HIV was first isolated and identified in 1983, and nearly 40 years later we still don't have a bona fide cure—although we're getting closer—but thanks to major advancements in antiretroviral therapy, most people who contract the disease can lead long and healthy lives. Some early advice about how to avoid the novel coronavirus was barely more than a best guess based on previous knowledge (for example, we now know that surface transmission of the virus is rare). In this issue's cover story, *Scientific American* editor in chief Laura Helmuth provides a definitive list of the hard-won certainties we've gleaned about COVID-19 in six short months (see "Nine Important Things We've Learned about the Coronavirus Pandemic So Far").

Also in this issue, Amy Maxmen profiles the global history of so-called pandemic games that epidemiologists use to model and predict how global diseases might arise and, most important, how we can prepare to mitigate them. Despite such exercises, she details how the U.S. has so badly bungled its handling of the virus (see "Two Decades of Pandemic War Games Failed to Account for Donald Trump"). She posits that powerful treatments and vaccines might be the solution for countries with rampant outbreaks. But of course, such remedies take time.

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Health & Medicine

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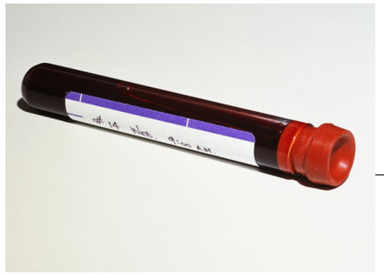
On the Cover

9 essential facts about the coronavirus pandemic

IRENE RINALDI



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Volume 2 • Number 5

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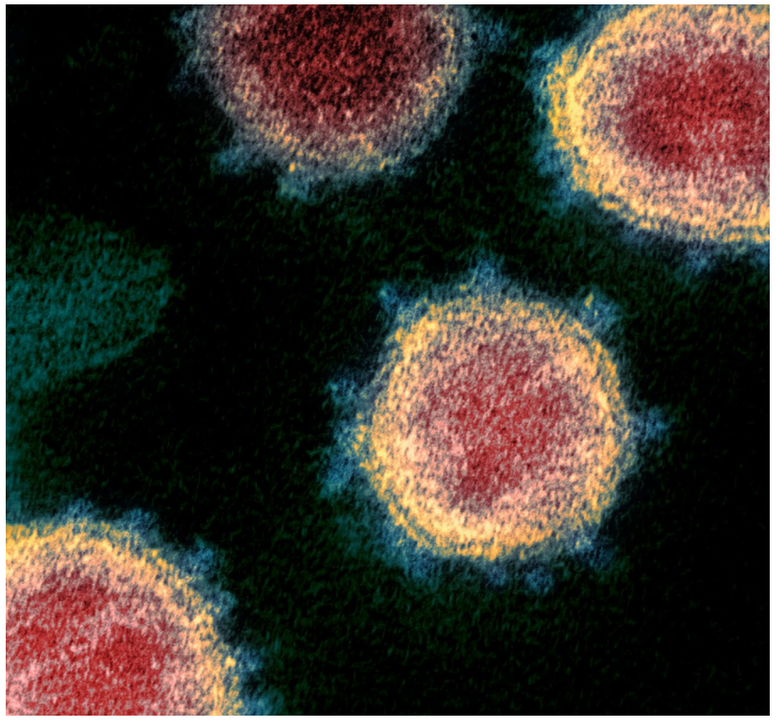

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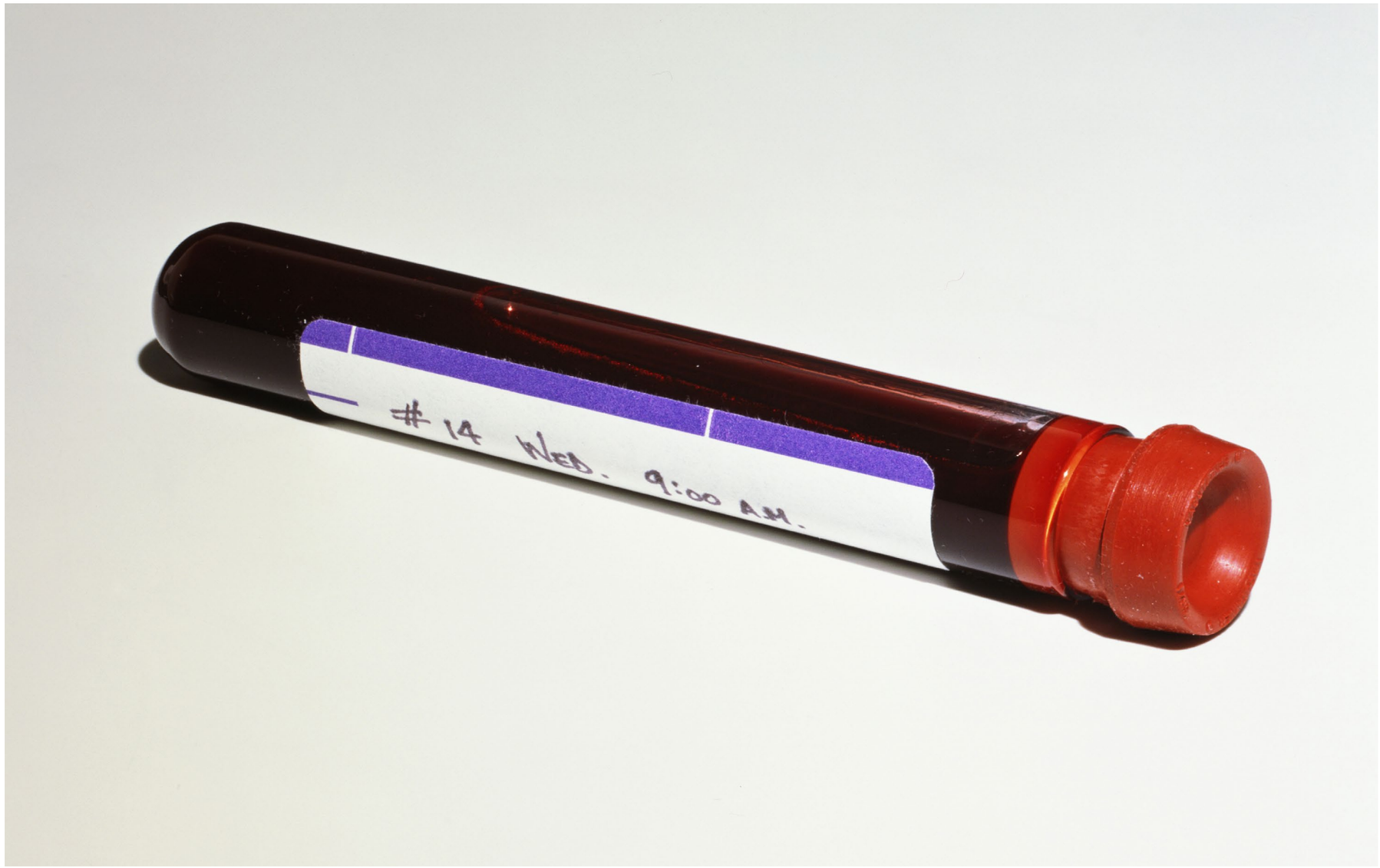

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Experimental Blood Test Detects Cancer up to Four Years before Symptoms Appear

The assay looks for stomach, esophageal, colorectal, lung and liver malignancies

For years scientists have sought to create the ultimate cancer-screening test—one that can reliably detect a malignancy early, before tumor cells spread and when treatments are more effective. A new method reported in July in *Nature Communications* brings researchers a step closer to that goal. By using a blood test, the international team was able to diagnose cancer long before symptoms appeared in nearly all the people it tested who went on to develop cancer.

"What we showed is, up to four years before these people walk into the hospital, there are already signatures in their blood that show they have cancer," says Kun Zhang, a bioengineer at the University of California, San Diego, and a co-author of the study. "That's never been done before."

Past efforts to develop blood tests for cancer typically involved researchers collecting blood samples from people already diagnosed with the disease. They would then see whether they could accurately detect malignant cells in those samples, usually by looking at genetic mutations, DNA methylation (chemical alterations to DNA) or specific blood proteins. "The best you can prove is whether your method is as good at detecting cancer as existing methods," Zhang says. "You can never prove it's better."

In contrast, Zhang and his col-

leagues began collecting samples from people before they showed any signs of cancer. In 2007 the researchers began recruiting more than 123,000 healthy individuals in Taizhou, China, to undergo annual health checks—an effort that required building a specialized warehouse to store the more than 1.6 million samples they eventually gathered. Around 1,000 participants developed cancer over the next 10 years.

Zhang and his colleagues focused on developing a test for five of the most common types of cancer: stomach, esophageal, colorectal, lung and liver malignancies. The test they developed, called PanSeer, detects methylation patterns in which a chemical group is added to DNA to alter genetic activity. Past studies have shown that abnormal methylation can indicate various kinds of cancer, including pancreatic and colon cancer.

The PanSeer test works by isolating DNA from a blood sample and measuring DNA methylation at 500 locations previously identified as having the greatest likelihood of signaling the presence of cancer. A machine-learning algorithm compiles the findings into a single score that indicates the probability of that person having the disease. The researchers tested blood samples from 191 participants who eventually developed cancer, paired with the same number of matching healthy individuals. They were able to detect cancer up to four years before symptoms appeared with roughly 90 percent accuracy and a 5 percent false-positive rate.

The new study "offers several interesting approaches in the quest for a blood-plasma-based cancer-screening test," says Colin Pritchard, a molecular pathologist at the University of Washington School of Medicine, who was not involved in the research. It will be important, though, for another research team to independently validate the findings in a different group of people before the test can be considered for clinical use, he says.

Usha Menon, a professor of gynecological cancer at University College London, who also did not participate in the study, observes that the method used by Zhang and his colleagues provides a robust, preliminary baseline test—an "essential first step" toward a commercial cancer-screening product. "The authors are not suggesting that they have a test that can be used clinically at this stage," she says. "They are clear that what they have is a robust preliminary demonstration of early detection of multiple cancer types four years prior to conventional diagnosis."

"We are still a ways away from having an accurate blood-based 'pan-cancer' screening test. But it is not impossible to achieve."
—Colin Pritchard

Most likely, such a test would first target high-risk populations, Menon says. And it would require devising a second panel of tests to enable clinicians to determine the specific cancer type and rule out false positives.

Zhang believes such a feature could be developed with more work, and he agrees that further studies are needed. Given the challenges in repeating an effort of this magnitude, a government-industry partnership, he says, would ideally undertake the follow-up research. An ideal test would target the most common cancers, as Zhang's study did, as well as the deadliest ones. "There are cancers where early detection can make a really big difference," he says. Pancreatic cancer, for example, is the next target Zhang and his colleagues are working on.

If and when cancer blood tests do become available, Pritchard warns, they probably will not be able to detect all cancers before they become symptomatic. "One cancer might have a very long lead time, where another is very short," he says. "Cancers that grow very quickly might not be detected even if someone is, for example, doing an annual screening." It is possible, too, that some types of malignancies may never be detected by blood tests because they do not produce a measurable signal in blood plasma.

"We are still a ways away from having an accurate blood-based 'pan-cancer' screening test. But it is not impossible to achieve," Pritchard says. "There are several large efforts underway, with some promise for the future."

—Rachel Nuwer

The Dentist Will See You Now: But Will You See the Dentist?

Dental practices are taking measures to keep patients safe. Some people are wary, however

PETER CADE GETTY IMAGES

Mary Lyn Koval did not want to go to the dentist. A marketing communications consultant in upstate New York, Koval works from home and felt she was staying safe during the coronavirus pandemic. One of her childhood fillings had broken, however. “I put off going for two weeks. But I was afraid that if I’d exposed a cavity, it would devolve into a series of root canals” instead of a simple filling replacement, she says. Dental offices were then still closed by state order. Yet urgent and emergency procedures were allowed. Should Koval have chosen to delay treatment and risk a root canal—or, worse, a tooth extraction? Or should she have risked exposing herself to COVID-19 at the dentist’s office? These questions are all part of the new pandemic calculus.

All states have now allowed dental practices to resume elective procedures (New York started doing so on June 1). Yet dentists know many patients remain scared of coming in. Indeed, many dentists and hygienists are afraid, too. “It’s such a high-risk profession,” says Grant Ritchey, a dentist with a private practice in Tonganoxie, Kan. “You’re in people’s mouths. You’re 18 inches from their faces. You’re creating aerosols.” Aerosols are tiny droplets that hang in the air and can contain the coronavirus. They can be produced when a dental worker uses compressed air and water in your mouth. Ritchey says he has adopted the mindset that “everyone is infected.” Even before he had to close his office, he started taking extra precautions such as having patients wait in their car instead of the waiting room and taking everyone’s temperature—although not all people infected with the coronavirus have a fever. Since reopening, he has ramped up gradually—seeing fewer patients than usual, spacing out appointments and disinfecting surfaces more frequently.

When Koval finally called her dentist about her tooth, she asked about the safety protocols in place. And when she went in, she thought the staff followed precautions very carefully. “I was repeatedly asked if I felt comfortable,” she says. “They were explaining the protective procedures as we went along.”

Dentists are taking extra care. But a lot of these measures are simply extensions of their normal regimens. “At dentist offices, we were doing universal protections—such as disinfection and PPE [personal protective equipment]—before it was cool,” says Matthew Messina, a consumer adviser and spokesperson for the American Dental Association. Access to PPE was the main limiting factor for Messina in reopening his Columbus, Ohio–based practice when the state gave the green light. In recent months many dentists have donated much of their supply of protective gear to medical workers treating coronavirus patients on the front lines.

Ritchey says the association has been doing “a phenomenal job under trying times.” It has put out guidelines for reopening. And it has held frequent briefings to keep members updated on new research, as well as on recommendations from the U.S.

Centers for Disease Control and Prevention and the World Health Organization.

There are still plenty of unknowns about coronavirus transmission. And those uncertainties are playing out in dentists' offices across the North American continent. In Ontario, a dispute is brewing between dentists and dental hygienists over the necessity of wearing highly protective N95 masks, according to the Canadian Broadcasting Corporation. The hygienists say N95s should be required for any task that might produce aerosols, whereas the dentists assert that surgical masks are sufficient.

And the pandemic itself is causing dental problems. Michelle Augello, a dentist in Buffalo, N.Y., has noticed an uptick in people complaining of issues such as headaches and jaw pain since the pandemic started. "In the morning, they practically have to force their mouth open, to unclench," she says. "Or they feel like there's an imprint of teeth on the side of their tongue"—from pressure through the night.

There is no one-size-fits-all treatment for jaw pain because a spectrum of things can cause it. Augello ticks through the various approaches: ibuprofen and icing, stress management, jaw exercises and myofascial massage. A night guard worn in the mouth can help with teeth grinding and jaw clenching. Sometimes a more serious jaw-joint problem is revealed.

Melissa Leebaert had her own set of calculations to make. Leebaert, a voice-over professional in Bethesda, Md., had a hip-replacement surgery postponed because of the pandemic. Going through with it could have further delayed a routine dental cleaning because she had been told she would have to wait at least three months after surgery to see the dentist. Both procedures would increase the risk of infection, and the wait would mitigate that risk. So Leebaert decided to get her teeth cleaned sooner rather than later after Maryland allowed dental practices to reopen on May 7. "It was important—not like going for a pedicure," she says.

Messina agrees. "Proper oral health is an integral part of overall health," he says. During a routine visit, he explains, dentists are, of course, looking for cavities and gum disease. But they are also screening patients for oral cancers and other conditions. "Most people see their dentist more frequently than their doctors," Messina says. Tartar buildup—that stuff the hygienist scrapes off your teeth during a cleaning—can lead to inflammation of the gums, which can worsen inflammatory conditions such as diabetes, arthritis and cardiovascular disease. "Having your teeth cleaned can lower the inflammatory load on the body," he adds.

Ritchey, who has written about the lack of hard scientific evidence for the standard six-month cleaning, is sympathetic. "Some patients are not ready," he says. "They may be concerned for their own health, or they're caring for an elderly relative, or they are fearful. They're erring on the side of caution." Ritchey's appointment scheduler is working through the backlog, calling patients who are due for a cleaning. If they decline, she slides them down the list to be called in another couple of months. People who are fairly healthy may safely delay a routine dental cleaning, Ritchey says. If you have no gum disease and little decay, you can put off your cleaning for up to six months with low risk because most dental problems progress slowly. If you regularly have dental issues or are not otherwise healthy, however, dental problems can progress more quickly, he says. A three- to six-month delay can mean that instead of a filling, you need a crown—or that instead of a crown, you need a root canal or an extraction.

Beyond routine checkups, if you have any pain, swelling or bleeding, you should call your dentist. "We can help you determine if yours is an emergency, an urgency or not a big deal," Messina says, adding that several of his patients have sent him photographs of their problems—which he calls "tooth selfies."

If you do not have a regular dentist, you can still get a consultation and care. Many dental offices take emergency patients. And those that do can often be found through an online search for "emergency dental services."

Koval, who got her tooth repaired during New York's shutdown, is still wary and plans to put off her next routine cleaning. Although the number of COVID-19 cases in New York is declining, unlike those in many other states, she says she worries about a possible spike. "I'm going to wait and see for now," Koval says.

—Jill U. Adams

Babies' Mysterious Resilience to Coronavirus Intrigues Scientists

COVID-19 is often mild in infants. Learning why could help scientists better understand the disease—and point the way toward possible treatments

GETTY IMAGES

As the new coronavirus continues to burn through populations, studies are beginning to shed light on its impact on infants. And so far the findings have been promising for parents and researchers alike.

The initial data suggest that infants make up a small fraction of people who have tested positive for COVID-19. A Centers for Disease Control and Prevention study released in April reported 398 infections in children under one year of age—roughly 0.3 percent of all U.S. cases at that time for which age was known. In addition, most of these cases appear mild in nature: a review published in April in the *Italian Journal of Pediatrics* that looked at infants up to the age of six months found that those who were infected typically exhibited only a slight cough, runny nose or fever that disappeared in a week or so. Other studies have suggested similar, minor reactions. The question is: Why?

One of the favored hypotheses focuses on how easily the new coronavirus can gain access to the body's tissues. Infection occurs when particles of the virus, SARS-CoV-2, enter human cells through a receptor called ACE2 and hijack those cells' machinery to make copies of themselves. The copies then invade new cells. The thinking is that infants' cells have only a few ACE2 receptors, whereas those of an elderly person might harbor thousands. With fewer available points of entry in a baby, it could be harder for the virus to break in. Alternatively—and perhaps counterintuitively—an infant's immune system might simply be too immature to attack SARS-CoV-2. Given that most of the damage in severe COVID-19 cases seems to be caused by strong immune responses, that immaturity may work in babies' favor.

The latter possibility could even explain a subtlety in the data: although infants appear resilient to COVID-19, they might be at marginally higher risk than older children. Early data from China suggested that 10.6 percent of infected chil-

dren younger than one year had severe or critical illness—a rate that decreased dramatically with age. "It's a dance that takes place between the virus and our own immune system," says Rana Chakraborty, a pediatric infectious disease specialist at the Mayo Clinic. If the body's defenses react too little, the virus will be able to take over. An overreaction can be equally deadly, however. So children older than about one year might be in a sweet spot between infants, whose immune systems have not yet fully kicked in, and adults, whose defenses are sometimes overzealous.

Indeed, the April CDC study similarly found that infants younger than one year account for the highest percentage of hospitalizations among young children. But Leena B. Mithal, a pediatric infectious disease specialist at Northwestern University, argues that this trend could simply be because all newborns taken to a hospital routinely undergo a full examination to ensure that they do not have an underlying bacterial infection—a process that can take days. She conducted a study involving 18 infants younger than 90 days who tested positive for SARS-CoV-2 at the Ann & Robert H. Lurie Children's Hospital of Chicago and found that although half of the babies were hospitalized, none required intensive care. "I think that is reassuring, that young infants actually may not be at a specifically higher risk of severe and critical illness as we initially were worried about," Mithal says.

Although some of the details still need to be teased out, it is clear that infants are uniquely resilient to COVID-19—a finding that could aid in treatment-development efforts. Scientists have already identified drugs that block certain inflammatory pathways in the body, and several are in clinical trials in COVID-19 patients. Another possibility is that drugs that target the ACE2 receptor could be the key to a vaccine or treatment.

Scientists have also hypothesized that children are more likely to have recently been infected with other coronaviruses, which could provide cross-protective antibodies. Or maybe the answer comes down to the fact that infants and older children often do not yet have underlying health problems. "That would give them a better head start—at least biologically," says Aimee Ferraro, a senior core faculty member at the School of Health Sciences at Walden University.

"Parents should be aware that it's important to protect children not [just] from the infection itself—because it's mild—but also from this postinflammatory syndrome."
—Asif Noor

The high rate of mild cases in infected children seems promising—both for researchers who would like to target treatment and for anxious parents. But the data remain limited, and experts continue to be cautious. It is important to remember that we simply do not know the long-term consequences of COVID-19, Ferraro says. This ignorance is evident in a number of cases in which youngsters initially became mildly sick with the disease and later developed a potentially life-threatening condition known as multisystem inflammatory syndrome in children, or MIS-C, in which various organs become inflamed. Although this phenomenon has occurred mostly in children older than one, Mithal argues that it is too early to tell whether infants can develop it.

"Parents should be aware that it's important to protect children not [just] from the infection itself—because it's mild—but also from this postinflammatory syndrome," says Asif Noor, a clinical assistant professor of pediatrics at New York University, who specializes in infectious diseases in children. With that warning in mind, he advises that parents should limit visitors during a baby's first few months and ask that everyone—even those who are asymptomatic—stand at least six feet away from the newborn. Although informing grandparents that they cannot hold their new grandchild might be heartbreaking, he argues that doing so is undoubtedly for the best. And Ferraro notes that cases among newborns might appear lower for the sheer reason that many have been shielded from the world—family members included—since the beginning of the pandemic. "I think this is a new normal," Noor says.

—Shannon Hall

Trash-Collecting Researchers Find Dietary Patterns in Discarded Hair Clippings

People in low-income neighborhoods eat more proteins from animals and fewer from vegetables, a study suggests

Poorer people in the U.S. tend to have less access to nutritious foods than the wealthy. Measuring the dimensions of the problem can be tricky because diet research often depends on inaccurate surveys and requires contacting hundreds, if not thousands, of people.

A study published in August in the *Proceedings of the National Academy of Sciences USA* reports on an unorthodox approach to more easily assess how meat and plant consumption varies among communities of differing socioeconomic status—and, potentially, how dietary patterns change over time.

Specifically, to look at how people consume their protein, the authors collected discarded hair from barbershops and hair salons. Different foods have different ratios of isotopes, or variants of a particular element, that end up as parts of amino acids—protein building blocks in our body, including in our hair.

The researchers analyzed ratios of carbon and nitrogen isotopes in the samples to determine the form of dietary protein people consumed, and they compared their findings with U.S. Census data on socioeconomic status. In North America, meat has very different carbon and nitrogen ratios than vegetables. And carbon ratios further indicate whether consumed meat came from corn- or grass-fed animals.The study found that in areas with lower socioeconomic status, corn-fed animal proteins, which are often found in fast food, were more common than plant proteins in the average diet.

Across all populations, animal proteins made up more than 55 percent of the diets analyzed. Yet in lower-income populations, that figure was as high as 75 percent. The researchers determined the affluence of each community by looking at the cost of living, the mean household income and the average price of a haircut in a given zip code.

TED MORRISON *GETTY IMAGES*

Isotopes have long been examined to measure human and natural activity. Besides looking at diet, study co-author James Ehleringer, a biologist and geophysics researcher at the University of Utah, has used isotope ratios to explore questions about counterfeit labeling in coffee beans, lawn management and unidentified remains in forensic investigations since the 1990s.

Some of the data in the new study go back to 2008, when Ehleringer and his colleagues published a paper showing that hydrogen and oxygen isotope ratios in people's hair could be mapped to where they drank water in the contiguous U.S. Last year he decided to use some of the data from that earlier study—along with new research—to look at diet patterns that could be deduced by examining hair.

Ehleringer and University of Utah

professor Thure Cerling put together a low-budget team that consisted of academic colleagues and even some family members. Ehleringer's wife, Edna, and Cerling's college-age children, Claire and Dylan, were eager to take a road trip. The team randomly selected barbershops and hair salons within a particular zip code. As was the case for the 2008 study, they got approval from business owners to take hair from their garbage. The researchers sorted what they gathered from each shop into clusters that they thought might be tied to a particular individual. But no attempt was made to identify a salon patron—nor did Ehleringer and his colleagues use the hair clippings to pinpoint a person's age, gender, travel or health status.

The team ultimately ended up with samples from 65 cities in the central and western U.S. It also took them from 29 zip codes in Utah's Salt Lake Valley to get an intensive look at an urban area. Hair isotope ratios varied within a somewhat narrow range, but it was still possible to correlate them with living costs in specific zip codes, enabling the finding that people in lower-income areas consumed more meat. (Earlier research had established isotope values that could be used to identify diets ranging from vegan to meat-heavy.)

One surprise came when the investigators realized that the levels of carbon isotopes in samples from the Salt Lake Valley could be linked to prices for a haircut, depending on a zip code's socioeconomic level. They also calculated trends in body mass index for some zip codes and found that isotope ratios were linked to higher obesity rates in lower-income areas.

Although he is not a nutrition expert, Ehleringer points to research tying meat consumption to negative health consequences. Using discards from barbershops and hair salons, he hopes, will provide experts in the field with an inexpensive means of studying dietary patterns on a large scale. "Our easy-to-use 'stable isotopes in hair' approach provides a means for community assessments that are free of the more typical survey-based approaches," Ehleringer says. "Our hope is that the health community will consider this kind of assessment in [its] efforts to obtain large-scale [dietary] patterns. The analysis cost is less than $10 per person, making it affordable."

Some recent data suggest that red meat and the saturated fat that comes with it may not be as harmful as previously thought. But plenty of studies link animal-based foods—particularly processed meats such as hot dogs, bacon, bologna and salami—with a variety of health risks.

Contributing to the problem, Ehleringer and many health experts contend, is the question of access. Massive industrial feedlots, or "concentrated animal feeding operations," have made cheap protein much more available in the U.S.—a trend that differs from those in other countries. "In Brazil, it is the more economically advantaged people that have greater access to meats," Ehleringer points out. (He was a co-author of a study published this year that examined isotope ratios in fingernail clippings from Brazilians to determine what was in their diet.)

Harvard University nutrition and epidemiology professor Qi Sun says this study is an important contribution to the field of socioeconomic determinants of diet quality. Research such as Ehleringer's, he hopes, should encourage the U.S. government to adopt strategies to improve the affordability and availability of healthy foods in poorer populations. "This study may help the policy makers allocate resources to the socioeconomically disadvantaged communities for not only information dissemination but also assistance in eventually reducing their animal intake," Sun says.

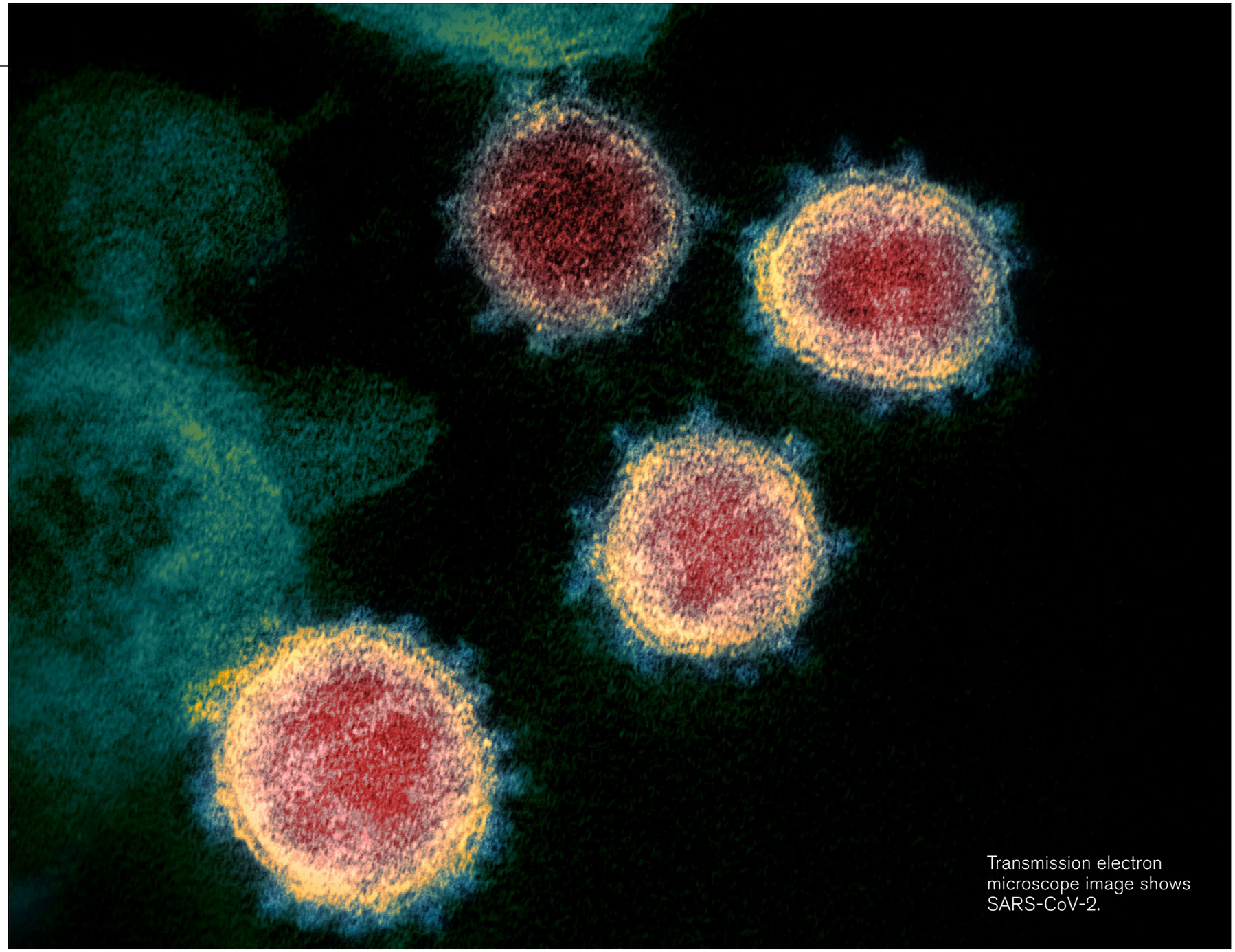
For the first time in decades, global meat production is on the decline—as is meat consumption in the U.S. But Sun asserts that too much red meat is still being consumed. He is heartened, though, by the food industry's exploration of plant-based meat alternatives, including the Impossible Burger and the Beyond Burger. Red meats such as beef, lamb and pork, as well as processed meats, Sun says, should have little or no role in a healthy diet because obesity is so widespread and is associated with diabetes, heart disease and early mortality.

Cerling says that the researchers' intention was to use the tools they had to help address poor nutrition in the U.S. "Better access to information is needed," he says. "And our hope is that our study provides additional information so that policy makers can make an informed judgment."

—Bret Stetka

Second Coronavirus Strain May Be More Infectious–but Some Scientists Are Skeptical

Researchers question whether a mutant viral strain that infected more cells in a lab dish is necessarily more transmissible among humans



Transmission electron microscope image shows SARS-CoV-2.

GETTY IMAGES

The hubbub around mutations in the virus that causes COVID-19—and how they might make it more infectious—has been around since the early phase of the pandemic. A preprint study about a particular mutation involving the "spikes" studding the SARS-CoV-2 pathogen drew attention, and that investigation has now been peer-reviewed and published in *Cell*. The paper details a change in one amino acid in the virus that may have made it more infectious. But virologists are far from reaching a consensus about the possible role of this mutation.

The paper indicates that a single amino acid change from D (aspartic acid) to G (glycine) on the SARS-CoV-2 spike protein (which the virus uses to grab on to human cells) is the key to how infectious the pathogen is. "The spike protein has a critically important role in the biology of the virus," says Bette Korber, a computational biologist at Los Alamos National Laboratory and lead author of the new paper.

Korber and her colleagues came to this conclusion after employing multiple approaches to examine the two strains. First they performed a statistical analysis that showed how the mutant virus—referred to as the G strain—achieved dominance across multiple continents, outperforming the coexisting original ver-

sion of SARS-CoV-2, the D strain. Then the researchers tested the amount of the virus in individuals with COVID-19 at hospitals in the Sheffield Teaching Hospitals NHS Foundation Trust in England. The results showed that the G strain produced more of the virus in the human body than the D strain. But the former did not lead to a higher hospitalization rate, meaning it apparently did not cause more severe illness. Finally, the team members created "pseudotype" pathogens by embedding SARS-CoV-2 spike proteins containing either D or G amino acids into other disease-causing viruses. They tested these pseudotype viruses by infecting human cells in a lab dish, and the result suggested that the G-bearing one was more infectious. Examining cells in a dish, however, is not the same as testing them using "multiple cell types with an immune system in a human body," says Emma Hodcroft, a molecular epidemiologist at the University of Basel in Switzerland, who was not involved in the study. "We just have to be really careful with how far we take the conclusions."

The study authors say they are not arguing that current vaccine and therapeutic efforts, most of which are based on the original D strain, will be useless. "But it means that we need to carefully check [the effects of the mutation] and make sure there is no impact," Korber says. "You want to be certain [therapies and vaccines] work well against today's virus, not just yesterday's virus."

Meanwhile some scientists worry that the results are being overinterpreted. Nathan Grubaugh of Yale University and his colleagues published a paper in *Cell* on the same day as Korber's study to lay out limitations to—and alternative explanations for—its findings. Others debated Korber and her colleagues' conclusions via social media when their paper was first released as a preprint.

Grubaugh's paper points out that when one strain is simply more prevalent, that does not always mean it is more infectious. The researchers write that the higher frequency of the G strain "may be explained by chance." They add that "there is good evidence that for SARS-CoV-2, a minority of infections are responsible for the majority of transmission" and that most of the infections that seeded outbreaks may have happened to involve the G strain. It is also possible that the strain (which emerged in Europe) traveled farther and more frequently to other parts of the planet, leading to its global dominance. "That's kind of the disentangling that's really difficult," Hodcroft says, noting that there are too many factors in play.

"The spike protein has a critically important role in the biology of the virus."
—Bette Korber

As for the amount of virus detected in the human body, the method Korber's team used "doesn't measure infectious virus, and that's all that matters for transmission," says Vincent Racaniello, a virologist at the Vagelos College of Physicians and Surgeons at Columbia University, who was not involved in either of the two *Cell* papers. In viral infections, he says, "you have a period where you're actually producing infectious virus. But then the infection basically stops. And then what are left are degraded viruses that persist in your body for a long time." The technique employed by Korber and her colleagues can detect degraded viruses, "so that's not a good enough experiment to prove that this is driving transmission," he adds.

Whether the G strain could affect the efficacy of potential vaccines and therapeutics is still unknown. The paper by Korber's team shows that antibodies from people who had been infected with SARS-CoV-2 fight against both strains. "That was a really encouraging step, although more work needs to be done," she says.

The debate over the newly identified mutation and its implications is likely to continue because several preprint papers suggest that the G strain might be more infectious. But Korber's study is the only one to do so that has been peer-reviewed so far.

"These back-and-forths between scientists—they really are normal, and this is how science evolves," Hodcroft says. "It isn't an indication that all of science is in disagreement.... If you [surveyed] scientists, they would give you the same general ideas about the virus."

"I'm not saying that what they're suggesting is not plausible," Racaniello says. "This could be proven one day, and I would be fine with that."

—Karen Kwon

Strongest Evidence Yet Shows Air Pollution Kills

The finding comes as the Trump administration has been rolling back clean-air regulations

As California's Camp Fire raged in 2018, soot and other pollution filled the skies. Particulate matter concentrations widely surged above 12 micrograms per cubic meter ($\mu g/m^3$), pushing them into the Environmental Protection Agency's "unhealthy" range. And in some places, they jumped to hundreds of $\mu g/m^3$.

This miasma included particles 2.5 microns in diameter or smaller, known as PM2.5, which also spew from tailpipes and smokestacks as cars burn gas and power plants combust coal. Their minuscule size lets them travel deep into the lungs, causing short-term breathing problems. Thousands of previous studies show such particles can also exacerbate asthma in the long term and contribute to cardiovascular problems, low birth weight and other issues. There is widespread medical consensus on this association, but some members of an EPA committee overhauled by a Trump administration appointee, along with oil and gas industry consultants, claim the studies did not show direct causality. Harvard University biostatistician Francesca Dominici and her colleagues address such assertions in a study published in July in *Science Advances.* They say their investigation shows the most comprehensive link between air pollution and premature deaths yet.

Typical air-pollution studies use only regression analysis, a statistical method designed to sort out the likelihood that a particular factor (such as air pollution) influences an outcome—in this case, mortality. But it is not always clear whether such models adequately account for other possible influencing factors. In the new paper, Dominici's team instead used five separate statistical approaches (including regression analysis) with a data set of 570 million observations collected over 16 years from 68.5 million Medicare enrollees. This technique helped to distinguish effects of particulate pollution from other influences. It effectively mimicked a randomized experiment (the gold-standard test for teasing out cause and effect), which would be unethical to conduct in this kind of investigation. "This area of statistics has never been applied to air pollution and mortality," Dominici says.

Bay Bridge is obscured as smoke from the Camp Fire fills the air in San Francisco on November 15, 2018.

MICHAEL SHORT *GETTY IMAGES*

The results show that tightening the allowable PM2.5 level from 12 to 10 $\mu g/m^3$ could lower mortality risk in the elderly by up to 7 percent—saving more than 143,000 lives in a decade.

The study impressed others in the field, including C. Arden Pope III, an air-pollution expert at Brigham Young University, and John Bachmann, a former associate director at the EPA's air-quality office. "In terms of size, in terms of statistical power and in terms of analytic sophistication, this is as good as it gets," Pope says.

The findings come as the Trump administration has been rolling back air-pollution regulations. In April the EPA proposed keeping PM2.5 rules unchanged, after what the agency says was a careful review and consultation with its science advisers. Before the review was completed, however, EPA administrator Andrew Wheeler dismissed an auxiliary panel of advisers that typically provides scientific expertise on such matters. The whole collection of air-pollution studies is powerful, Bachmann says, and "this [new] one as a topper is a pretty potent response" to the EPA's proposal.

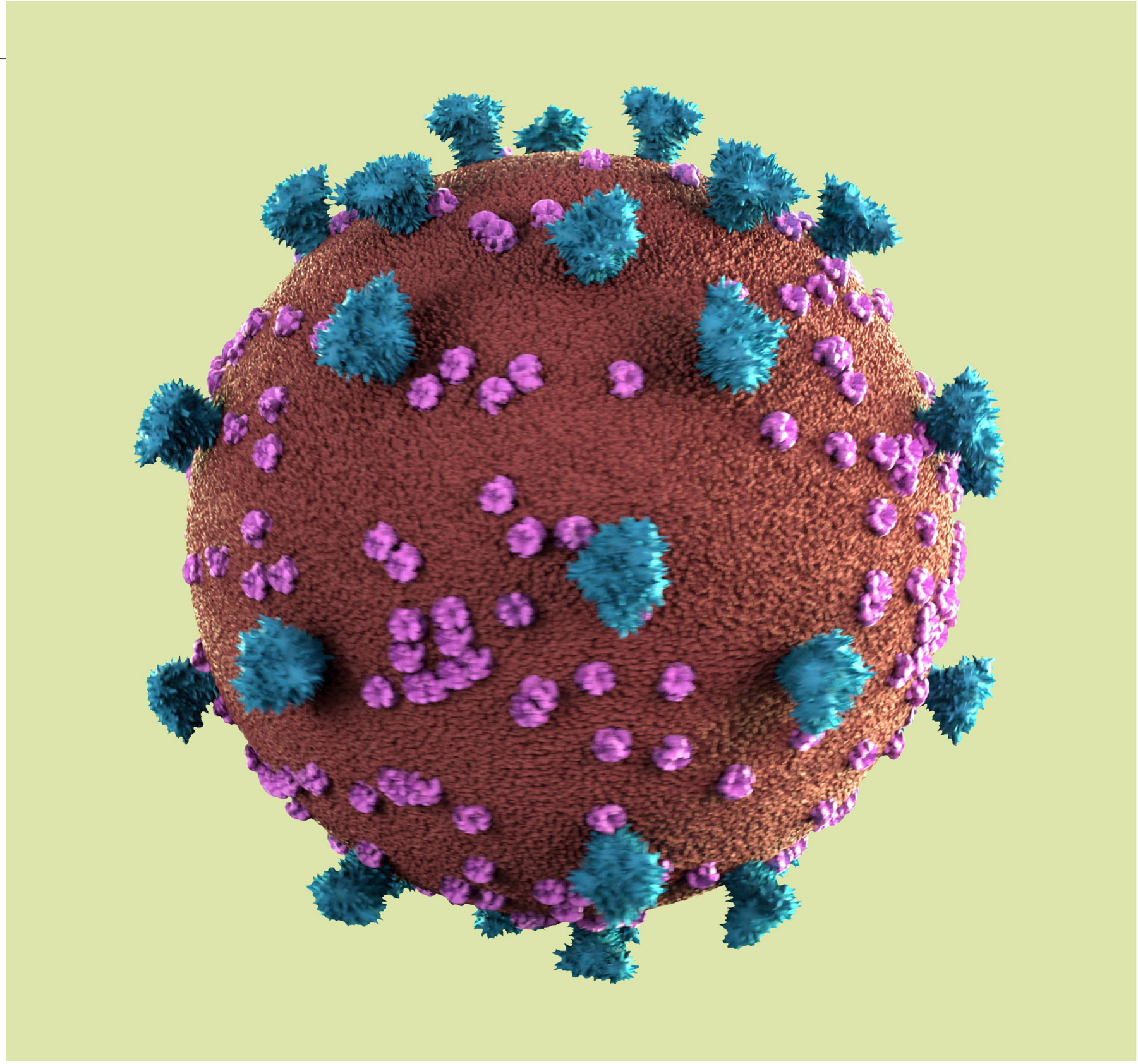
—*Susan Cosier*

Concerns about Waning COVID-19 Immunity Are Likely Overblown

The decline seen in some studies is normal, experts say. But scientists must wait to see whether infection confers long-term protection

COVID-19 triggers a strong immune response in most people. Yet several recent studies showed that the amounts of antibodies in those recovering from the virus appear to decline within a few months of infection. The findings set off a frenzy of speculation that immunity to the virus may not last long, throwing cold water on hopes for a vaccine. Many scientists say such worries are overblown, however.

A study conducted with a small group of patients in China, published online on June 18 in *Nature Medicine,* showed that in both asymptomatic and symptomatic individuals with COVID-19, antibody levels dropped significantly during recovery—and the levels became undetectable in 40 percent of the asymp-



JOSEP GUTIERREZ *GETTY IMAGES*

tomatic group. A preprint study by researchers in England that was posted online in mid-July similarly demonstrated that antibody levels declined substantially within a few months of infection and that people with less severe illness had fewer antibodies. And most recently, a small study, published on July 21 in the *New England Journal of Medicine,* found a "rapid decay" in antibodies among individuals with mild cases of COVID-19.

These results may sound universally grim. But several experts *Scientific American* spoke with said they thought that the declines were not as scary as initially portrayed, that some reduction in antibodies is normal and expected and that antibodies are just one piece of the immunity puzzle. Evidence from other viruses and from animal studies of SARS-CoV-2 infection provides reason for optimism, they add. That assessment is no doubt reassuring for vaccine developers, some of whom are already racing ahead with large-scale clinical trials. Only longer follow-up studies of people infected with the novel coronavirus will show whether antibodies confer lasting protection, however.

The human immune system consists of two parts: The innate immune system mounts a nonspecific response to invaders that occurs within hours of infection. In contrast, the adaptive immune system launches a targeted reaction to a particular pathogen that can take weeks or months to develop. The latter system consists of three parts: antibodies, B cells and T cells. Together they recognize and fight off the invader and can store a memory of it in case of future infection (vaccines similarly work by creating a fake "memory"). Some of the antibodies, known as neutralizing antibodies, can bind to a specific part of a pathogen and deactivate it. Scientists hypothesize that these antibodies' presence in people who have had COVID-19 may be one key signal of immunity.

The recent studies documenting patients' antibody decline have triggered some scary headlines proclaiming that any immunity to COVID-19 may be short-lived. In the *NEJM* study, Otto Yang, a professor of medicine and associate chief of infectious diseases at the David Geffen School of Medicine at the University of California, Los Angeles, and his colleagues measured antibodies in 34 people, the large majority of whom had clinically mild coronavirus infections, at an average of 37 and 86 days after symptoms appeared. "What we saw was that the amount of antibodies against the virus dropped very dramatically in that time period"—by about half every 36 days, he says. (The paper originally described a half-life of 73 days, but this figure was found to be a mathematical error.) Yang adds a few caveats: Scientists do not know whether antibodies are protective against SARS-CoV-2 infection—although that possibility is a reasonable guess—or how much protection they might confer. And they are not certain they are measuring the right type of antibodies. Nevertheless, he says, "the decline that we see is strikingly fast."

Other scientists interpret the decline as less worrisome and in line with that observed for other viruses. In reference to the *NEJM* study, Florian Krammer, a professor of microbiology at the Icahn School of Medicine at Mount Sinai, tweeted, "I fail to see the rapid decay here." Using a test developed by Krammer and his team, a preprint study led by his colleague Ania Wajnberg found a much more modest decrease in antibodies. In some cases, people who had fewer antibodies at first even showed a small increase over time.

Seeing a slight reduction in antibodies is fairly normal, says Wajnberg, an associate professor at the Icahn School of Medicine. "Frankly, that's not that surprising, because you're not sick anymore," she says. Once a person has successfully fought off the infection, you would expect his or her antibodies to approach a lower, baseline level. If that individual were reinfected, the B cells could then ramp up the number of antibodies again, Wajnberg says. Or maybe that baseline level itself would prove enough to be protective. "What we don't want to see is: two weeks later, [antibodies] go to zero. Honestly, that would be very unexpected," Wajnberg adds. But the fact that antibodies wane over time is not shocking, she says.

Viral immunologist Zania Stamataki agrees. "The data on the decline of the antibodies are not scary. We're seeing a tiny drop, which is quite expected," says Stamataki, a senior lecturer at the University of Birmingham's Institute of Immunol-

ogy and Immunotherapy in England. "I don't think there is this really rapid decay like people have reported."

Yang stands by his interpretation of a steep decline, saying it agrees well with the *Nature Medicine* study and the English preprint paper. He says the disagreement may reflect the populations being studied. Yang and his colleagues looked at people with clinically mild infections who had lower initial levels of antibodies, whereas those who have higher levels to start with "may actually also have more persistent antibodies," he says.

Stamataki and others caution that it remains to be seen whether any level of antibodies can shield against reinfection. "The fact that we can pick up antibodies in patients who have been infected with coronavirus does not mean that they are protected," she says. "It means that they can recognize the virus and make the right immune response that could potentially be protective in the future." Researchers still do not know what amounts and types of antibodies will prevent reinfection six or seven months later, "but we will soon find out," she adds.

Scientists have focused on antibodies because they are relatively easy to measure with a blood test and may be helpful as a treatment for COVID-19. But the adaptive immune system also involves T cells, which may mount a strong response to the novel coronavirus even if antibodies have waned. In May, Alessandro Sette and Shane Crotty, both at the La Jolla Institute for Immunology, published a study showing that SARS-CoV-2 produces a strong T cell response, particularly to the virus's "spike" protein, which it uses to gain entry to cells. And a study by researchers at the Karolinska Institute in Sweden found such responses in people with mild or asymptomatic COVID-19, including when antibodies were undetectable.

So even without antibodies, T cells could keep a record of the infection. But its strength may depend on that infection's severity. "The memory is proportional to the perturbation to the insult—how much of a scare the immune system has," Sette says. "If it's a very mild infection, it might not create enough of an immune response in the first place to create a long-lasting memory." In fact, Stamataki says, it is possible that some people may clear SARS-CoV-2 using the innate immune system—without developing any memory of it. If they then encountered the virus again, they could potentially get COVID-19 a second time.

"The data on the decline of the antibodies are not scary. We're seeing a tiny drop, which is quite expected."
—Zania Stamataki

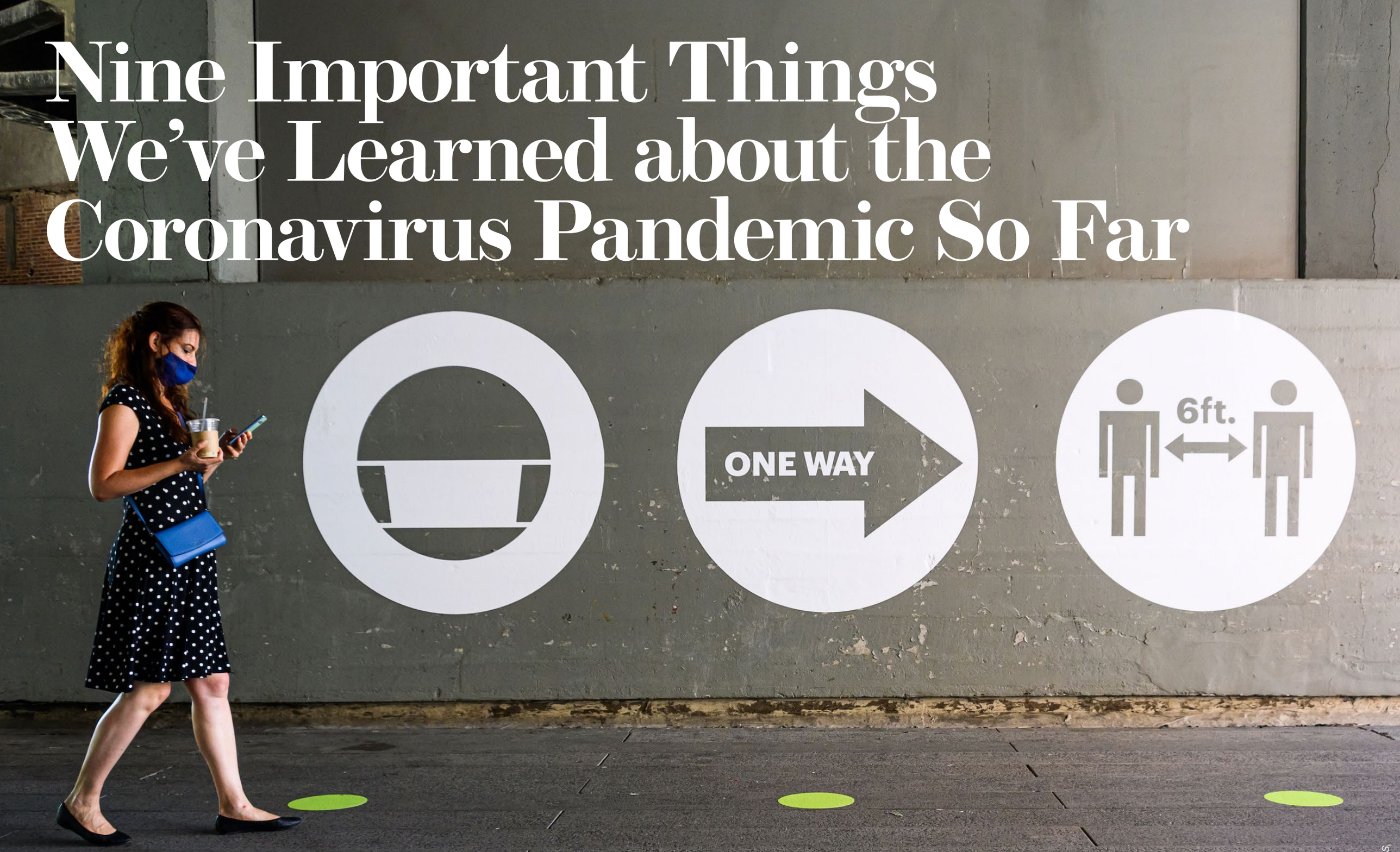
There have been a number of anecdotal reports of people getting reinfected with the novel coronavirus, but no substantive proof has been established. There are other explanations: people with weak immune systems might not be clearing the virus totally, or tests might be picking up remnants of it that are not infectious, Stamataki says. Although true reinfection is not impossible, it would probably occur in only a small minority of people, she adds.

Scientists still do not know what level of immune response might be protective against future infection. Only longer-term studies will be able to answer that question. Wajnberg says her colleague Viviana Simon, a professor of microbiology at the Icahn School of Medicine, is currently leading a study to monitor a few hundred health care workers, with and without antibodies, over the course of a year or two to see who gets COVID-19 and who does not. Yang says he and his team plan to continue monitoring more than 60 people for a year as well.

In the short term, though, animal research offers some clues. One study found that monkeys that were previously infected with the novel coronavirus and developed antibodies did not get sick when they were later reexposed. But monkeys are not humans, of course. And deliberately exposing people to the virus raises clear ethical issues, so we will likely have to wait for more data to accumulate over the next few months. "We need to be patient," Sette says.

—Tanya Lewis

Nine Important Things We've Learned about the Coronavirus Pandemic So Far



Some early public health messages about COVID-19 have been overturned

By Laura Helmuth

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Laura Helmuth is editor in chief of *Scientific American.*

WE'RE IN A TERRIFYING AND CONFUSING PANDEMIC, WITH NEW AND sometimes conflicting information about COVID-19 emerging all the time. In the early days, a lot of public health advice was based on what we knew about previous disease outbreaks. But this new coronavirus behaves in unexpected ways, and it is hard to keep up. What's more, people tend to remember the first things they learn about a new subject, a phenomenon called anchoring bias, and it is psychologically challenging to replace old information with new knowledge. Here are nine of the most important things we have learned about SARS-CoV-2 in the past seven months and why we did not fully understand or appreciate them at first.

Outbreaks of COVID-19 can happen anywhere. There was a lot of wishful thinking and othering (as in: it is those other people's problem) in the first months of the pandemic: Chinese people got it because of where they buy their groceries. Italian people got it because they greet one another with kisses on the cheeks. People on cruise ships got it because of the buffets. People in nursing homes got it because they are frail. People in New York got it because the city is crowded. Now we know that outbreaks can happen in urban areas, rural areas, suburbs and any culture around the world.

COVID-19 can sicken and kill anyone. The first victims of the pandemic were disproportionately older or had existing health conditions. Age and frailty are still risk factors for serious disease and death, but we now know the disease can kill young and healthy people. It can kill young adults. It can kill teenagers. It can kill children.

Contaminated surfaces are not the main danger. Early on, public health experts advised people to wash their hands frequently (while singing "Happy Birthday" twice), disinfect surfaces and avoid touching their face. This was based on studies of how other diseases spread, such as norovirus and viruses that cause the common cold. It is still a good idea to wash your hands regularly (and avoid handshakes), but now we know that surfaces are not the main vector for SARS-CoV-2.

It is in the air. At first experts thought the virus was spread primarily through globs of mucus and saliva expelled when people cough or sneeze. They thought these droplets were heavy enough to drop out of the air fairly quickly. Based on early cases of hospital spread, the virus seemed to be aerosolized—that is, lofted into the air in particles small enough to float—only by certain medical procedures such as placing someone on a ventilator. But we now know that the virus is expelled in a range of droplet sizes, with some particles small enough to persist in the air, especially in indoor, poorly ventilated spaces.

Many people are infectious without being sick. Other respiratory diseases make people cough and sneeze. The original SARS outbreak made people so sick so quickly that most of them went to the hospital. Temperature checks and telling sick people to stay home can stop symptomatic diseases from spreading, and in the first months of the pandemic, many countries started screening people at their borders to detect cases. But the biggest challenge for stopping SARS-CoV-2 is that many apparently healthy people spread the disease without symptoms or before symptoms start simply through talking and breathing.

Age and frailty are still risk factors for serious disease and death, but we now know the disease can kill young and healthy people. It can kill young adults. It can kill teenagers. It can kill children.

Warm summer weather will not stop the virus. Influenza is a seasonal respiratory disease that peaks in the winter, and some experts hoped the spread of COVID-19 would show a similar pattern and slow in the Northern Hemisphere during the spring and summer. Now we know that people's behavior, regardless of season, is the strongest predictor of whether the disease will spread.

Masks work. When the pandemic began, experts worried that mass mask buying could exacerbate shortages of personal protective equipment for health care workers and others who needed it. They also warned that masks might make people complacent about social distancing and that cloth or paper masks (unlike N95 surgical masks) cannot stop the smallest aerosolized viral particles. Now we know that masks can greatly reduce the amount of virus people expel into the air while speaking and that masks protect people who are wearing them—not perfectly, but enough to reduce transmission of the disease.

Racism, not race, is a risk factor. The pandemic should put an end to the common misconception that race, a social construct, is a biological explanation for health disparities. COVID-19 has disproportionately killed people of color in the U.S. This is not because of genetic differences but because of systemic racism that has isolated and impoverished many Native American people and made Black and Latinx people more likely to have "essential" jobs that expose them to infection, a greater burden of stress and less access to high-quality health care.

Misinformation kills. The U.S. president, other politicians, antivaccine activists and members of the right-wing media, to their everlasting shame, have used the pandemic to stoke racism, spread misinformation and amplify conspiracy theories. Their followers have threatened health officials, including Anthony Fauci, along with his family; refused to wear masks; refused to cooperate with contact tracers; and rejected proven basic public health advice about social distancing. U.S. Representative Louie Gohmert of Texas, who refused to wear a mask in the Capitol and reportedly discouraged his staff and interns from wearing masks, tested positive for SARS-CoV-2 and was treated with hydroxychloroquine, a drug that President Donald Trump has endorsed but that has failed in clinical trials. Trump supporter Herman Cain died of COVID-19 on July 30, weeks after attending a rally in Tulsa, Okla., without a mask. Calls to poison-control centers spiked after Trump speculated that injecting or ingesting disinfectants could protect against the coronavirus. Early evidence suggests people who watched Fox News were more likely to downplay the pandemic, worsening the spread. The most important public health measure during a pandemic of a disease with no cure or vaccine—as many countries around the world that have controlled the virus have shown—is to help experts share clear, trustworthy, accurate, actionable information based on the best evidence. Spreading lies has spread this disease.

Two Decades of Pandemic War Games Failed to Account for Donald Trump

The scenarios foresaw leaky travel bans, a scramble for vaccines and disputes between state and federal leaders, but none could anticipate the current levels of dysfunction in the U.S.

By Amy Maxmen

BRENDAN SMIALOWSKI *GETTY IMAGES*

Amy Maxmen is a Brooklyn-based science journalist whose work appears in *Nature, Smithsonian,* Nova/PBS and other outlets.

LIKE ALL PANDEMICS, IT STARTED OUT SMALL. A NOVEL CORONAVIRUS emerged in Brazil, jumping from bats to pigs to farmers before making its way to a big city with an international airport. From there, infected travelers carried it to the U.S., Portugal and China. Within 18 months the coronavirus had spread around the world, 65 million people were dead, and the global economy was in free fall.

This fictitious scenario, dubbed Event 201, played out in a New York City conference center before a panel of academics, government officials and business leaders in October 2019. Those in attendance were shaken—which is what Ryan Morhard wanted. A biosecurity specialist at the World Economic Forum in Geneva, Switzerland, Morhard worried that world leaders were not taking the threat of a pandemic seriously enough. He wanted to force them to confront the potentially immense human and economic toll of a global outbreak. "We called it Event 201 because we're seeing up to 200 epidemic events per year, and we knew that, eventually, one would cause a pandemic," Morhard says.

The timing, and the choice of a coronavirus, proved prescient. Just two months later China reported a mysterious pneumonia outbreak in the city of Wuhan—the start of the COVID-19 pandemic that has so far killed more than 800,000 people.

Morhard was not the only one sounding the alarm. Event 201 was one of dozens of simulations and evaluations over the past two decades that have highlighted the risks of a pandemic and identified gaps in the ability of governments and organizations around the world to respond.

The exercises anticipated several failures that have played out in the management of COVID-19, including leaky travel bans, medical-equipment shortages, massive disorganization, misinformation and a scramble for vaccines. But the scenarios did not anticipate some of the problems that have plagued the pandemic response, such as a shortfall of diagnostic tests and world leaders who reject the advice of public health specialists.

Most strikingly, biosecurity researchers did not predict that the U.S. would be among the hardest-hit countries. On the contrary, last year leaders in the field ranked the U.S. top in the Global Health Security Index, which graded 195 countries in terms of how well prepared they were to fight outbreaks on the basis of more than 100 factors. President Donald Trump even held up a copy of the report during a White House briefing on February 27, 2020, declaring: "We're rated number one." As he spoke, SARS-CoV-2 was already spreading undetected across the country.

Now, as COVID-19 cases in the U.S. approach six million, with more than 180,000 deaths, the country has proved itself to be one of the most dysfunctional. Morhard and other biosecurity specialists are asking what went wrong—why did dozens of simulations, evaluations and white papers fail to predict or defend against the colossal missteps taken in the world's wealthiest nation? In contrast, some countries that had not ranked nearly so high in evaluations, such as Vietnam, executed swift, cohesive responses.

The scenarios still hold lessons for how to curb this pandemic and for how to respond better next time. Deadly pandemics are inevitable, says Tom Frieden, a former director of the U.S. Centers for Disease Control and Prevention. "What's not inevitable is that we will continue to be so underprepared."

MORE THAN A GAME

Pandemic simulations first started gaining popularity in the 2000s. Biosecurity and public health specialists took their cue from war-game exercises used by the military in an effort to stress-test health systems, see what could go wrong and scare policy makers into fixing the problems. In these roundtable events, academics, business leaders and government officials made real-time decisions to deal with an expanding crisis laid out in television-news-style reports.

Two early simulations involved biological attacks in which other countries unleashed smallpox in the U.S. Operation Dark Winter, in 2001, and Atlantic Storm, in

2005, were orchestrated by biosecurity think tanks in the U.S. and attended by influential leaders such as Gro Harlem Brundtland, the former head of the World Health Organization, and Madeleine Albright, the secretary of state under former president Bill Clinton.

During the course of Dark Winter and Atlantic Storm, participants found that power struggles between federal and state leaders bogged down a health response as the epidemic doubled and quadrupled. Hospitals were unable to handle the influx of people requiring care, and national vaccine stockpiles ran dry. Tom Inglesby, director of the Center for Health Security at Johns Hopkins University, which helped to lead both of the exercises, says that along with the fresh memory of terrorist and anthrax attacks in 2001, these events encouraged the U.S. Congress to act. Not long after the Dark Winter exercise, the U.S. government committed to developing a national supply of smallpox vaccines. And in 2006 Congress passed the Pandemic and All Hazards Preparedness Act to improve the nation's public health and medical response capabilities in the event of an emergency. This included funding for research on emerging infections.

Anxiety about pandemics was also rising internationally. Not long after the 2003 outbreak of severe acute respiratory syndrome (SARS) spread to more than two dozen countries and killed 721 people in mainland China, Hong Kong and Taiwan, the 194 member states of the WHO agreed to bolster the world's defenses against health threats through a set of rules called the International Health Regulations. These included commitments by countries to invest in pandemic preparedness and to report outbreaks to the WHO so that other nations could be alert. The regulations were put to the test in 2009, when an H1N1 influenza virus is estimated to have killed more than 100,000 people, and again in 2013, with the spread of Middle East respiratory syndrome (MERS). Then came the world's largest outbreak of the Ebola virus, in 2014–2016, which killed around 11,000 people—roughly half of those infected.

A Taiwanese soldier disinfects a street on May 12, 2003, in the Wanhua area in Taipei, where an apartment complex with some 140 homes had been quarantined after an elderly man died of severe acute respiratory syndrome (SARS).

PATRICK LIN *GETTY IMAGES*

In response to the drumbeat of epidemics, the United Nations commissioned a panel to explore how the world could better prepare for future threats. The resulting 2016 report made several recommendations, including investment in vaccines, therapeutics and diagnostics for emerging infectious diseases—and a need for "all relevant responders" to take part in infectious disease simulations.

In January 2017 the World Bank and the Bill & Melinda Gates Foundation backed a pandemic simulation at the World Economic Forum in Davos, Switzerland—a gathering of global leaders in business, politics and academia. The exercise highlighted a need for better coordination among companies, governments and nonprofit organizations when it came to managing global supply chains for medical equipment, diagnostic tests, treatments and vaccines. The scenario coincided with the launch of an Oslo-based foundation to develop and distribute vaccines for emerging infections, called the Coalition for Epidemic Preparedness Innovations (CEPI). It has received funding from the Gates Foundation, the U.K. biomedical charity Wellcome and countries such as Japan and Germany. At the same time, Morhard and his colleagues set about

building a network that would coordinate logistics and regulations globally, such as those associated with the use of potential new treatments, if an epidemic caught hold. "We were working on that when this pandemic hit," Morhard says. "But it's become clear that all the things we worked on were not commensurate to what we need."

FALSE SECURITY

As these global efforts were underway, Inglesby felt that his own country was not devoting enough attention to preparing for a pandemic. The fact that the U.S. saw relatively few deaths from MERS and Ebola might have given policy makers a false sense of security, he says.

In May 2018, with leaders in the White House and Congress who had never dealt with a major epidemic, Inglesby and his colleagues at Johns Hopkins hosted an exercise in Washington, D.C., called Clade X. It featured a respiratory virus that was engineered in a laboratory. One early lesson of this simulation was that travel bans did not stop the virus from gaining ground. Infections spread rapidly below the radar because half of the people infected showed few or no symptoms. Medical supplies ran short, and hospitals were overwhelmed. Federal and state leaders issued conflicting messages. More than 20 months passed before a vaccine was available.

Six top-line recommendations emerged from the exercise. These included reducing vaccine production time and creating a "robust, highly capable national public health system that can manage the challenges of pandemic response." Some argue, however, that this emphasis was misplaced in subsequent discussions. Jeremy Konyndyk, a senior fellow at the Center for Global Development in Washington, D.C., says that members of the biosecurity community have often focused on vaccines rather than on the complex, systemic deficiencies in the public health system. They often overlooked the "middle game" in outbreak responses. "We have a strong end game once there is a vaccine, and we have a strong opening game if countries contain an outbreak when case numbers are low," he says. But insufficient attention is devoted to harnessing and coordinating enough health workers and biomedical resources to efficiently test people, treat them, find their contacts and quarantine them. This is precisely the conundrum that the U.S. finds itself faced with right now.

"We have a strong end game once there is a vaccine, and we have a strong opening game if countries contain an outbreak when case numbers are low."
—Jeremy Konyndyk

Clade X and other simulations did capture the challenge of the missing middle game. For example, in an exercise conducted by the U.S. Department of Health and Human Services last year, dubbed Crimson Contagion, tourists returned from China with a new flu virus that took hold in Chicago and infected 110 million Americans (the exercise assumed the pathogen was more contagious than SARS-CoV-2 is). Disorganization deepened at local, state and federal levels as leaders scrambled to implement policies and procure equipment.

A report that followed the simulation noted that the HHS—the agency that oversees the CDC and the Food and Drug Administration—does not have clear authority to lead a federal response to a pandemic or access to the funds to roll out such a response. But as with CladeX, the discussion after the simulation focused on straightforward end game strategies such as vaccine development rather than the more complicated strengthening of the national public health system.

Still, at least Clade X and Crimson Contagion highlighted governmental weaknesses. These shortcomings were less apparent in the Global Health Security Index and in a complementary effort overseen by the WHO, called the Joint External Evaluation. When it came to detecting new pathogens, this ranking commended the U.S. for its laboratory networks and "an extensive commercial market" for diagnostic tests.

As the coronavirus pandemic gained speed this year, it became clear that the U.S. needed more than exceptional lab capacity and legions of epidemiologists to contain the spread of the virus.

THE RECKONING

By late January, Inglesby was anxious. The coronavirus outbreak was escalating at a frightening pace in China and spreading to other countries, including the U.S. These were the kinds of foreboding signs that he had plugged into his simulations. But the Trump administration seemed to view the outbreak as China's problem, Inglesby says. During the third week of January, Trump posted one reassuring tweet about the coronavirus and around 40 regarding his impeachment hearings, his rallies and defeating the Democrats. The only public action that the government took was to screen travelers coming from China for symptoms at a handful of international airports.

Inglesby knew that travel bans and checkpoints do not sufficiently prevent the spread of contagious pathogens. So, on January 26, he listed a series of actions needed to prepare the U.S. for the coronavirus—dubbed nCoV—in a 25-part Twitter thread. "Global and national leaders should be looking ahead to what must be done to prepare for the possibility nCoV can't be contained," he wrote. The list included vaccine development, expansion

of personal protective equipment for health care workers, and "very high numbers of reliable diagnostic tests."

These actions are key to curbing most infectious diseases, but in an outbreak they must occur at hyperspeed. Biosecurity experts had woven this lesson into every simulation because muddling the response in the early months of an epidemic has catastrophic repercussions. J. Stephen Morrison, director of global health policy at the Center for Strategic and International Studies in Washington, D.C., says: "You can't fart around for weeks on end and then give a confused, half-baked, not very serious response."

Infectious disease researchers were also worried. Fearing undetected transmission in the U.S., scientists in the states of Washington, New York and California started vetting tests that detect the genetic sequence of the virus in late January—including a protocol developed by German researchers and disseminated by the WHO. But their efforts to roll tests out for public use hit a wall at the FDA, which was not ready to authorize them. Meanwhile officials at the CDC insisted that labs exclusively use tests that it had developed.

The CDC started shipping test kits to public health departments on February 6. On a Sunday morning, three days later, Kelly Wroblewski, the infectious disease director at the Association of Public Health Laboratories in Silver Spring, Md., woke up to a flood of e-mails saying that the tests did not work. "We always knew laboratory testing was complicated, but it's something that was often overlooked in these simulations," says Wroblewski; she had participated in Crimson Contagion just months earlier.

While the CDC scrambled to fix the faulty tests, labs lobbied for FDA authorization to use tests that they had been developing. Some finally obtained the green light on February 29, but without coordination at the federal level, testing remained disorganized and limited. And

"The best public health program is a program that uses real-time data to make real-time decisions. Real life is our exercise."
—Tom Frieden

despite calls from the WHO to implement contact tracing, many city health departments ditched the effort, and the U.S. government did not offer a national plan. Beth Cameron, a biosecurity expert at the Nuclear Threat Initiative in Washington, D.C., which focuses on national-security issues, says that coordination could have been aided by a White House office responsible for pandemic preparedness. Cameron had led such a group during Barack Obama's presidency, but Trump dismantled it in 2018.

In March the CDC stopped giving press briefings and saw its role diminished as the Trump administration reassured the public that the coronavirus was not as bad as public health experts were saying. An editorial in the *Washington Post* in July by four former CDC directors, including Frieden, described how the Trump administration had silenced the agency, revised its guidelines and undermined its authority in trying to handle the pandemic. Trump has also questioned the judgment of Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases and a leading scientist on the White House Coronavirus Task Force.

Confusion emerged in most pandemic simulations, but none explored the consequences of a White House sidelining its own public health agency. Perhaps they should have, suggests a scientist who has worked in the U.S. public health system for decades and who asked to remain anonymous because the person did not have permission to speak to the press. "You need gas in the engine and the brakes to work, but if the driver doesn't want to use the car, you're not going anywhere," the scientist says.

In contrast, New Zealand, Taiwan and South Korea showed that it was possible to contain the virus, says Scott Dowell, an infectious disease specialist at the Gates Foundation, who spent 21 years at the CDC and has participated in several simulations. The places that have done well with COVID-19 had "early, decisive action by their government leaders," he says. Cameron agrees: "It's not that the U.S. doesn't have the right tools—it's that we aren't choosing to use them."

THE END GAME APPROACHES

Perhaps the biggest limitation of simulation exercises was that they did not actually drive policy makers to prioritize and fund improvements to the public health system. Morrison now questions whether it is even possible to do that through simulations alone or whether people must experience an epidemic firsthand.

After more than 70 people in Taiwan died as a result of SARS in 2003, the government mapped out its emergency-response network. "Every year since then, for the past 17 years, they've held annual outbreak exercises and practiced, practiced, practiced," Morrison says. When the first coronavirus cases were reported in mainland China, Taiwan's well-oiled systems quickly kicked into gear. Despite its proximity to the outbreak, Taiwan has had only seven deaths from COVID-19 so far.

Now the U.S. has experienced a tragedy, too. The daily number of new COVID-19 cases broke records throughout much of July, after many states attempted to reopen their economies. Frieden says that one of the most crucial actions now is for health departments to strengthen their response systems by analyzing data in real time, so

that they can tailor interventions as needed. “The best public health program is a program that uses real-time data to make real-time decisions,” he says. “Real life is our exercise.”

But the end game that received the most attention in the aftermath of many simulations—drugs and vaccines—might indeed be the only way out for countries such as the U.S. and Brazil that have failed to contain the virus. Here, too, the simulations have warned about the disjointed efforts of governments and businesses. Biosecurity experts hope that CEPI and other initiatives to coordinate research and assistance will finally pay off.

Looking forward, many hope that the mistakes in handling the coronavirus will spur a fundamental reset in how U.S. policy makers think about pandemic preparedness. This means restructuring health systems, empowering public health leaders and ensuring that all components function in unison in the event of a crisis.

Toward the end of the Event 201 exercise in New York City last year, participants watched a mock news report forecasting that financial turmoil would last for years or even a decade. But societal impacts—including loss of faith in government and the media—could last even longer. The TV reporter signed off with a question: “Are we as a global community now finally ready to do the hard work needed to prepare for the next pandemic?”

The pandemic in that simulation failed to convince policy makers to act. It remains to be seen whether this one will.

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Sunny Dooley is one of the last traditional Diné storytellers. She lives in Chi Chil Tah, N.M., and has been telling the Diné Hozho (Blessing Way) stories for more than three decades.

POLICY & ETHICS

Coronavirus Is Attacking the Navajo "Because We Have Built the Perfect Human for It to Invade"

A traditional Diné storyteller explains how disadvantage and injustice have shaped her people's encounter with COVID-19

Native Americans of the Navajo Nation pick up supplies at a food bank in Casamero Lake, N.M., on May 20, 2020.

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As told to *Scientific American* in July 2020:

When a family member dies, we the Diné, whom Spanish conquistadors named the Navajo, send a notice to our local radio station so that everyone in the community can know. Usually the reading of the death notices—the names of those who have passed on, their ages, where they lived, and the names of their matrilineal and patrilineal clans—takes no more than five minutes. It used to be very rare to hear about young people dying. But this past week I listened to 45 minutes of death notices on KGAK Radio AM 1330. The ages ranged from 26 to 89, with most of the dead having been in their 30s, 40s or 50s.

I am in shock. The virus entered our community in March through a Nazarene Christian revival in Arizona. They brought in vanloads and busloads of people from across the Navajo Nation for the gathering; then all those vans and buses returned them to their respective communities, along with the virus. There were immediate deaths because the medical facilities were not ready for it. More than 500 Navajos have already died of COVID-19, and the disease is still spreading.

I am a Diné storyteller and keeper of traditions. I live alone in a hogan, a traditional octagonal log

house, in Chi Chil Tah, meaning “where the oaks grow,” after the Gambel oaks indigenous to this region. Officially known as Vanderwagen, the community lies 23 miles south of Gallup, N.M. The pandemic reached the area in late April. On May 1 the governor of New Mexico invoked the Riot Control Act to block off all exits into Gallup to stop the spread of the virus, and only residents could get in. The lockdown extended to May 11. It was not so bad the first week, but then we started to run out of food and water.

The groundwater in parts of Vanderwagen is naturally contaminated with arsenic and uranium; in any case, few of us have the money to drill a well. Usually my brothers and my nephew haul water in 250-gallon tanks that are in the back of a pickup truck. At Gallup they have a high-powered well; you pay $5 in coins, put the hose in your tank and fill it up. You haul that home, dump that into your cistern, and you have water in your house. Without access to Gallup, people began to run out of water—even as we were being told to wash our hands frequently.

My hogan has electricity but no running water. My brothers bring me water, and they put it in a 75-gallon barrel. I drink that water, and I wash with it, but I also buy five gallons of water for $5 in case I need extra. I typically use a gallon of water a day for everything—cooking, drinking and washing up. My great-grandmother used to say, “Don’t get used to drinking water, because one of these days you’re going to be fighting for it.” I have learned to live on very little.

We have a lot of cancers in our community, perhaps because of the uranium. And we have many other health issues that I think make this virus so viable among us. We have a lot of diabetes because we do not eat well. And a lot of heart disease. We have alcoholism. We have high rates of suicide. We have every social ill you can think of, and COVID has made these vulnerabilities more apparent. I look at it as a monster that is feasting on us—because we have built the perfect human for it to invade.

Days after Gallup reopened, I drove there to mail a letter. Every fast-food establishment—McDonald’s, Kentucky Fried Chicken, Wendy’s, Burger King, Panda Express, Taco Bell, all located on one strip—had long, long lines of cars waiting at their drive-throughs. This in a community with such high rates of diabetes. Perhaps there wasn’t any food available in the very small stores located in their communities, but I also think this pandemic has triggered a lot of emotional responses that are normally hidden. On the highway to Vanderwagen, there is a convenience store where they sell liquor, and the parking lot was completely full; everybody was just buying and buying liquor. There is a sense of anxiety and panic, but I also think that a lot of Navajo people don’t know how to be with themselves because there isn’t a really good, rounded, spiritual practice of any sort to anchor them.

COVID is revealing what happens when you displace a people from their roots. Take a Diné teenager. She can dress Navajo, but she has no language or culture or belief system that tells her what it means to be Diné. Her grandmother was taken away at the age of five to a BIA (Bureau of Indian Affairs) boarding school and kept there until she was 18. At school, they taught her that her culture and her spiritual practice were of the devil and that she needed to completely deny them. Her language was not valid: “You have a Navajo accent; you must speak English more perfectly.” Same happened to her mother. Our languages were lost; the culture and traditional practices were gone. That was also when spankings and beatings entered Diné culture. Those kids endured those horrible ways of being disciplined in the BIA schools, and that became how they disciplined their own children.

I meet kids like this all the time—who don’t know who they are. For 35 years I have been trying to tell them, You come from a beautiful culture. You come from one of hundreds of tribes who were thriving in the Americas when Columbus arrived; we had a viable political and economic system that was based on spiritual practices tied to the land. Some 500 years ago Spanish conquistadors came up the Rio Grande into North America in search of gold. They were armed with the Doctrine of Discovery, a fearful legal document issued by the Pope that sanctioned the colonization of non-Christian territories. Then, in the mid-1800s, the pioneers came from the East Coast with their belief in Manifest Destiny, their moral right to colonize the land. As their wagons moved west, the Plains Indians were moved out and put on reservations. When your spiritual practice is based on the land you’re living on and you’re being herded away from what somebody else would call her temple, or mosque, or church, or cathedral—that’s the first place your spirituality is attacked.

My great-great-great-great-grandfather on my father's side was captured and taken on what we call the Long Walk to Fort Sumner. Initially about 10,000 Diné were rounded up, and many died on that walk, which took weeks or months, depending on the route on which they were taken. They were imprisoned for four years at Fort Sumner and released in 1868 because of the Civil War. At about the same time, my great-great-great-great-grandfather on my mother's side escaped from Colonel Kit Carson at Canyon de Chelly and traveled north with his goats. He came back down to this area at just about the time my great-great-great-great-grandmother escaped Spanish slavery. Slavery was introduced here by the Spanish—that's never talked about. The children born at Fort Sumner were taken into Spanish families to be slaves.

We had the flu epidemic in the 1920s, one of many viruses to invade our community. Then, in the 1930s, there was the Great Depression. We didn't know that was happening: we did not have money, but we had wealth in the form of sheep. And the government came in and killed our sheep in the Livestock Reduction program. They said the sheep were eroding the land, but I think they did it because the sheep made us self-sufficient, and they couldn't allow that. We had spiritual practices around our sheep. Every time we developed self-sufficiency and a viable spiritual practice, they destroyed it. My mother said they dug deep trenches, herded the sheep and massacred them.

A tuberculosis epidemic in the 1940s took away my mother's parents. My great-grandmother, a healer and herbalist, had hidden my mother from the government agents who snatched Diné kids to put them into BIA boarding schools. My mother became a rancher, a prolific weaver, a beautiful woman who spoke the language. She did not speak much English. She died at 96; my great-grandmother died at 104. Now, in our community in Chi Chil Tah, there are no more traditional healers; the oldest person is my great-grand-aunt, who is 78. I am the only traditional Diné storyteller.

Now that we are talking about issues of race in America, we need to also talk about the Native American tribes that were displaced. There is a reservation in upstate New York of the Iroquois people—all of 21 square miles. How much land were the Iroquois originally living on? Who was living in what is now Massachusetts? What about Pennsylvania? What about all the states under the umbrella of the U.S.? Whose land are you occupying? Abraham Lincoln ordered the massacre of 38 Dakota men the day after Christmas the same week he signed the Emancipation Proclamation; they call him Honest Abe. They don't talk about the dark side of things, and I think that is what COVID has revealed—the dark side. We see a police officer putting his full body weight on the neck of a Black man, and suddenly everybody goes, "Wow! What have we evolved to?"

It seems to me that COVID has revealed a lot of truths everywhere in the world. If we were ignorant of the truth, it is now revealed; if we were ignoring the truth, it is now revealed. This truth is the disparity: of health, well-being and human value. And now that the truth has been revealed, what are we going to do about it?

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BEHAVIOR & SOCIETY

What AIDS Taught Us about Dealing with COVID-19

It's foolhardy to assume that only some categories of people are at risk

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In the face of any new and infectious disease outbreak, our first reaction and natural hope is that we will be spared from the suffering. Despite the hard logic of increasing numbers of new infections and rising forecasts of total deaths, our tendency is to deny the reality around us. So many bad things already happen in the course of our lives—cars crash, tornadoes strike and hearts fail. Why add another to the list?

When AIDS emerged, people were content to think of it as a gay man's disease, something that happened to "them" and not to "us." While terror and anxiety gripped those in the gay community in the early 1980s, the rest of the country kept on with the status quo. Even when the HIV epidemic was fully upon us and millions were infected worldwide, the common belief in heterosexual America was that there was nothing to worry about and no need to change the lifestyles we had grown accustomed to. Whole books were written on the myth of heterosexual AIDS. We paid the price for such foolhardy thinking in tens of thousands of lives lost.

Today we see this same reasoning at play with COVID-19. Many think of the disease as something that afflicts the old and infirm, with the young and healthy protected from the worst of it. We see this at play each day in packed beaches, bars and restaurants across the country and, unfortunately, in the escalating rate of new infections. For those who fear infection, it is easy to widen the divide by blaming "them," the young and healthy, for putting "us" at risk. But the truth,

much like the truth behind the spread of HIV, is that those spreading the disease are only doing what is natural to all of us.

There is a sexual dynamic to COVID-19 that is often unmentioned—not just in terms of how sex and sexual activity can spread SARS-CoV-2 but also in terms of how human sexual behavior is driving people out of their homes and into bars. Anyone with a craving for a beer can quench their thirst in the safety of their home, but gratification comes less easily for other desires, especially when one is young, single and living alone.

The same lessons we learned in the midst of the HIV epidemic to help young people change their behaviors can also be applied to COVID-19 today: know your risk, know your partner and take the necessary precautions.

When it comes to knowing their risk, many young people are operating under the false assumption that even if they become infected, they will not become severely ill. Not only is this base assumption false—according to the CDC, up to 20 percent of people aged 20 to 44 end up hospitalized because of the disease—but even people with asymptomatic infections are left with serious damage from the disease. A study published in *Nature Medicine* showed that two thirds of those with no clinical signs of COVID-19 had "ground-glass opacity" in at least one lung. The long-term health effects of such damage are unknown, but it is possible that an asymptomatic infection today may lead to a lethal illness later in life. The more people understand the risk—young people especially—the greater the likelihood that they will take the steps necessary to protect themselves and others.

Knowing one's partner is a much more challenging task. With HIV, knowing your partner meant knowing their infection status and knowing and trusting the sexual history they provided. That was hard enough. With COVID-19, which spreads much more easily through casual contact, it now means knowing that all the people you spend time with in close quarters have been protecting themselves sufficiently over the previous two weeks to be undoubtedly COVID-19-free. With the high rates of infection in most communities today, this is nearly impossible.

With this in mind, all of us should assume that everyone around us is infected and able to pass on the disease. And all of us should therefore make sure we are taking the necessary precautions to keep ourselves and those we love COVID-19-free: wearing masks, physically distancing and limiting any interactions indoors.

In the absence of clear leadership and strong governance to bring us out of this crisis, our best and only hope to reduce the number of new COVID-19 infections is clear communication about the nature of the disease, the real risk of infection, and the steps that each of us can take to avoid infection and exposure. Although treatment for HIV was what finally helped us contain the epidemic, communication was the strongest tool in our arsenal as we waited for that medical solution to arrive. Fortunately, the ability to communicate is one of the defining traits of our species. I have faith we will again use it wisely to wrestle another deadly pandemic under control.

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POLICY & ETHICS

Health Care Is Long Overdue for a Social Justice Reckoning

Biases in the system put the lives and well-being of women and minorities at risk

KELLY DAVIDSON *GETTY IMAGES*

With protesters in many U.S. cities marching for justice, and with the Supreme Court delivering a historic ruling protecting gay and transgender workers from workplace discrimination, this summer is shaping up to be a watershed moment for equality in America. But whereas much of our national conversation is focused on urgent issues such as police brutality, it is time we acknowledged that American health care, too, is long overdue for a reckoning with systemic forms of discrimination that have a detrimental effect on the health and well-being of tens of millions of American women.

Take, for example, heart disease. It is the leading cause of death among women—but a 2012 survey conducted by the American Heart Association found that 44 percent of women were unaware of this, with the highest percentages of unawareness among Blacks and Latinas. Why this discrepancy? Why are so many women more concerned with, say, breast cancer than they are with heart disease, a condition that kills six times as many women every year?

The AHA has explored that question, too, and found that many women reported that their physicians seldom if ever talked to them about heart health and, in some cases, misdiagnosed obvious symptoms of heart disease as panic, stress or even hypochondria.

That is a blatant example of how inherent biases put women's lives at risk, but it is not the only one. Gender, the socially constructed roles and behaviors associated with being male or female, is very much a part of the so-called social determinants of health, which researchers now believe play a large part in determining a patient's well-being.

How do these factors—which include everything from poverty and literacy rates to social relations and expectations—affect men and women (including transgender individuals) and people of color differently? Why is one group more susceptible than another? The reasons include racist and sexist barriers embedded in our institutions and communities, whether we are aware of them or not.

We at Northwell Health have created our Center for Equity of Care that includes the division of Diversity, Inclusion and Health Literacy (DIHL), which establishes networkwide policies and procedures to ensure meaningful access to services, programs and activities to incorporate health literacy, language access and cultural competency as integral parts of the delivery of safe, quality patient-centered care. And at the Katz Institute for Women's Health, we address decades of sex- and gender-based disparities in health and health care delivery through a new model: one based on unique clinical programs, sex- and gender-focused research and community partnerships. Many other health systems have similar programs to tackle these issues.

Preliminary data, for example, suggest that women have been more economically disadvantaged than men as a result of the COVID-19 pandemic. That makes sense: Women are overrepresented in service-related jobs such as retail and hospitality, face higher risk of layoffs because of those jobs, and tend to fill more marginal and lower-authority jobs. The closure of schools and day care centers has massively increased child care needs, which has largely impacted working mothers. Gender-based domestic violence has increased as a result of heightened tensions in households at the same time that essential health-support services are being disrupted or made inaccessible as a result of the need to socially isolate.

Gender also plays a role in the scientific study and management of the pandemic. Most alarmingly, women scientists are underrepresented among investigators studying COVID-19—presumably in part because women scientists and physicians also have to manage household issues such as homeschooling their children—making it less likely that representative research questions are being asked. Preliminary data also suggest that countries with female leaders have been especially successful at managing the pandemic. We need more of these female leaders at the table to make decisions globally, whether it is through the World Health Organization or in talks with scientists working on vaccines.

When it comes to fighting disease and maintaining health, sex, gender and race matter. We need to design the right COVID-19 studies now to identify the reasons for the sex, gender and race disparities—and develop appropriate interventions. And we need to ensure that women and communities of color are represented in designing and implementing solutions.

Equitable health outcomes and the health of our society depend on it.

Sian Leah Beilock is president of Barnard College.

BEHAVIOR & SOCIETY

Why Young Americans Are Lonely

And what we can do about it

There is a reason the term "physical distancing" has not been used much during the coronavirus pandemic: although it is a more accurate description of what public health experts are trying to achieve than "social distancing," it fails to capture the loss that many of us feel as a direct result of being separated from other people.

Young Americans might be the loneliest of all. As a cognitive scientist and college president, I am worried about that.

Loneliness has been a growing problem for decades—with some estimating that 61 percent of adults in the U.S. feel it—and it has only been made worse by the COVID-19 lockdown. Over the past four months the requirement that we sequester ourselves whenever possible, venturing outside our homes only for essentials and maintaining a six-foot minimum distance from fellow shoppers or exercisers, has been frustrating—even painful. Although keeping to ourselves helps prevent coronavirus's spread, humans are social creatures, and prolonged isolation takes a toll on our mental health.

The BBC Loneliness Experiment, a large-scale global study, recently published its much anticipated results, revealing that self-reported loneliness is highest among young people, men and those in "individualistic" societies. And this loneliness can be seen in the brain. One study found, for example, that when mice, social creatures like ourselves, are forced to live alone in cages, the

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isolation changes their brains' basic architecture and causes nerve cells to shrink. A more recent study of what social distancing during the pandemic has been doing to humans identified that the neural underpinnings associated with isolation are similar to those of physical hunger: to say you are "starving for contact" is not far from the reality of what is happening in your body in neurobiological terms.

Loneliness—much like hunger or thirst—is a signal that we are lacking something. Prolonged social isolation can even contribute to heart disease, stroke or premature death.

Clearly, we humans need at least a few deep, meaningful relationships to maintain good mental health and keep loneliness at bay. But how many? And what are the steps to get us there?

Back in the 1990s, British anthropologist Robin Dunbar, upon discovering a correlation between primates' brain size and the social groups they formed, concluded that humans have the brainpower to maintain about five close relationships.

Most of us fall woefully short of that number, unfortunately. The average American's number of close confidants (individuals with whom we can discuss important matters) has been shrinking. Adults in the U.S. had three confidants in 1985, compared with just two in 2004. And approximately one in four Americans reported having no close confidants in 2004—an almost threefold increase from 1985.

More recent data show that one in five millennials have no friends at all. And a survey released in 2020 found that 71 percent of millennials and almost 79 percent of Gen Z respondents report feeling lonely—a significantly greater proportion than in other generations.

Loneliness—much like hunger or thirst—is a signal that we are lacking something. Prolonged social isolation can even contribute to heart disease, stroke or premature death.

Deep friendships are becoming rare, especially among the young.

But we can work on cultivating and maintaining relationships. Here are some brief steps we can take on this front:

Keep an open mind. It is easy to automatically rule out someone as a friend because of an age gap, divergent political perspectives or different taste in books, movies or music. Stop. Give everyone a chance. Even one common interest can serve as an avenue into another person's inner world and establish the foundation for a closer connection.

Be the friend you would like to have. Say yes to invitations, be reliable, and respond to texts, e-mails and voicemail messages in a timely way. Consider volunteering your time for worthy causes, which will position you to help others who may also be struggling with loneliness. Provide instrumental and emotional support and give your friends your full attention. Celebrate their accomplishments. Remember their birthdays and other important events. Listen to their troubles and provide a shoulder to cry on when needed.

Make yourself vulnerable and be the first to show trust. Share something personal about yourself and be courageous enough to extend the first invitation to an event or social outing (know that you might get turned down, just like when pursuing a romantic relationship).

Be compassionate with yourself. Expect to make a few mistakes when trying to establish new friendships. No matter how hard you try, you will eventually say or do the wrong thing. Keeping that in mind can help you to stop being your own worst critic. Try to be as understanding of your own missteps as you are of others' minor blunders. If appropriate, apologize. Then move on. A little self-compassion will make the whole process easier, especially when a budding friendship fizzles (you will not be everyone's cup of tea, and that's okay).

Connections with other people help us thrive as human beings and face the slings and arrows of daily life. No one needs to feel completely isolated—even when we are physically distancing. There are steps we can take to form (or cultivate) close bonds, whether in person or virtually.

SCIENTIFIC AMERICAN
Health & Medicine

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