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April–May 2021

Lasting Impacts

A surprising number of COVID-recovered patients deal with an array of troublesome symptoms, well after the disease is gone

Plus:

THE MOST WORRYING CORONAVIRUS VARIANTS

ALZHEIMER'S BLOOD TEST

FOREVER CHEMICALS IN U.S. DRINKING WATER

WITH COVERAGE FROM
nature

LIZ TORMES

The COVID-19 Postscript

In the early months of the COVID-19 outbreak individuals took to social media to connect with others who, like them, were experiencing a wide array of problems long after they'd recovered from the disease itself. Symptoms included lingering fatigue, shortness of breath, "brain fog" and recurring fevers. In the year since it was officially declared a pandemic, SARS-CoV-2, the coronavirus that causes COVID, has sickened or infected more than 100 million people worldwide and killed more than 2.5 million. And it leaves an insidious postscript: a vague collection of ailments that can persist for weeks, sometimes months, even in patients who experienced only mild symptoms. Some epidemiologists, writes physician Carolyn Barber, estimate that at the end of the pandemic we may have some five million COVID "long haulers" (see "The Problem of 'Long-Haul' COVID").

Particularly troubling, reports writer Stefani Sutherland, are neurological impacts of the virus that disrupt synaptic connections and interfere with brain function, affecting speech and upping the incidence of depression, anxiety and sleep disorders (see "COVID Can Cause Forgetfulness, Mania or a Stutter"). The good news is that vaccinations are well underway and will help curb viral transmission. But assessing, researching and ameliorating the consequences of the virus will be ongoing for a long time.

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Health & Medicine

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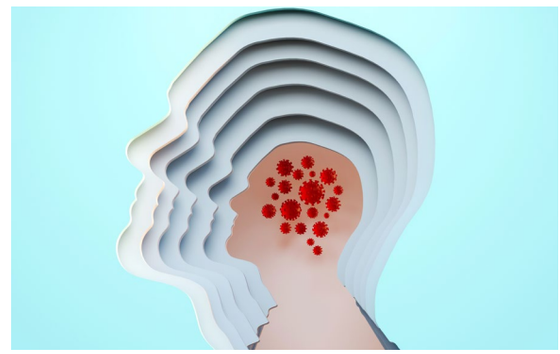

ANDRIY ONUFRIYENKO *GETTY IMAGES*

On the Cover

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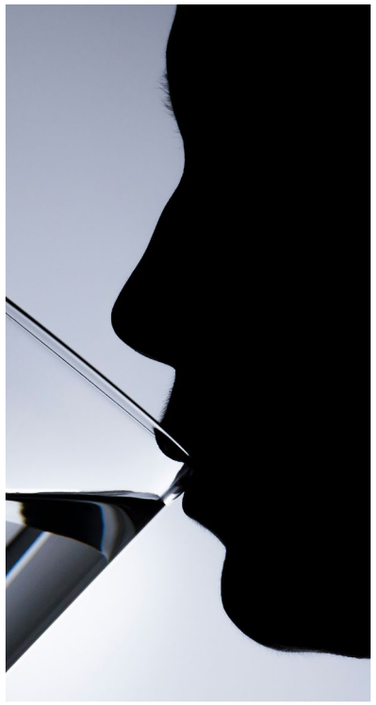
WHAT'S INSIDE

April–May 2021
Volume 3 • Number 2



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NEWS

FEATURES

OPINION

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Forever Chemicals Are Widespread in U.S. Drinking Water

Experts hope that with the Biden administration, the federal government will finally regulate a class of chemicals known as PFASs

Many Americans fill up a glass of water from their faucet without worrying whether it might be dangerous. But the crisis of lead-tainted water in Flint, Mich., showed that safe, potable tap water is not a given in this country. Now a study from the Environmental Working Group (EWG), a nonprofit advocacy organization, reveals a widespread problem: the drinking water of a majority of Americans likely contains "forever chemicals." These compounds may take hundreds, or even thousands, of years to break down in the environment. They can also persist in the human body, potentially causing health problems.

A handful of states have set about trying to address these contaminants, which are scientifically known as perfluoroalkyl and polyfluoroalkyl substances (PFASs). But no federal limits have been set on the concentration of the chemicals in water, as they have for other pollutants such as benzene, uranium and arsenic.

With a new presidential administration, experts say the federal government finally needs to remedy that oversight. "The PFAS pollution crisis is a public health emergency," wrote Scott Faber, EWG's senior vice president for government affairs, in a recent public statement.

Of the more than 9,000 known PFAS compounds, 600 are currently used in the U.S. in countless products, including firefighting foam, cookware, cosmetics, carpet treatments and even dental floss. Scientists call PFASs "forever chemicals" because their chemistry keeps them from breaking down under typical environmental conditions. "One of the unique features of PFAS compounds is the carbon-fluorine bond," explains David Andrews, a senior scientist at EWG. "That bond is incredibly strong." Ultimately this means that if PFASs enter the environment, they build up. These chemicals can linger on geologic time scales, explains Chris Higgins, a civil and environmental engineer at the Colorado School of Mines.

Because of their widespread use, release and disposal over the decades, PFASs show up virtually everywhere: in soil, surface water, the atmosphere, the deep ocean—and even the human body. The U.S. Centers for Disease Control and Prevention's Web site says that the agency has found PFASs in the blood of nearly everyone it has tested for them, "indicating widespread exposure to these PFAS in the U.S. population." Scientists have found links between a number of the chemicals and many health concerns—including kidney and testicular cancer, thyroid disease, liver damage, developmental toxicity, ulcerative colitis, high cholesterol, pregnancy-induced preeclampsia and hypertension, and immune dysfunction.

Concerned about PFASs' persistence and potential harm, Andrews and his EWG colleague Olga Naidenko set out to assess Americans' exposure to the chemicals via their drinking water. PFASs can get into this water in a variety of ways. For example, industrial sites might release the compounds into the water or air. Or they can leach from disposal sites. They can also percolate into groundwater from the firefighting foams used at airports and military bases. Andrews and Naidenko say there is a need for

"The PFAS pollution crisis is a public health emergency."
—Scott Faber

research into drinking-water levels because the federal government does not require testing water for PFASs. This leaves a gap in scientists' understanding of overall exposure. Andrews and Naidenko focused their analysis on two types of these chemicals—perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)—because those compounds had the most available data. The two researchers pulled that information together from various sources, including state agencies, the federal government and the EWG's own measurements.

The scientists estimated that more than 200 million people—the majority of Americans—have tap water contaminated with a mixture of PFOA and PFOS at concentrations of one part per trillion (ppt) or higher. Andrews and Naidenko say previous research shows that levels higher than 1 ppt can increase the risk of conditions such as testicular cancer, delayed mammary gland development, liver tumors, high cholesterol and effects on children's immune response to vaccinations. "It's a calculation of what would be a safe exposure level," Andrews says. Even when the researchers shifted their analysis to a higher level of 10 ppt, they still found some 18 million to 80 million Americans to be exposed. Representatives of the chemical industry have disagreed with such concerns. "We believe there is no scientific basis for maximum contaminant levels lower than 70 ppt," the American Chemistry Council said in statement to *Scientific American*.

Experts not involved in the new research, which was published recently in *Environmental Science & Technology Letters*, say these findings are exactly what they had expected—and that is troubling. "This is going to be kind of sad, but I wasn't at all surprised that they exist in many different water systems and that many, many people are getting exposed through their drinking water," says Jamie DeWitt, an associate professor of pharmacology and toxicology at East Carolina University's Brody School of Medicine.

Zhanyun Wang, an environmental scientist at the Swiss Federal Institute of Technology Zurich, raises concerns about how widespread this class of chemicals is. “It’s a little bit scary that it is so prevalent in the U.S., which has quite a big population,” he says. “Now that we know that PFASs have a rather low safety level.”

“This is going to be kind of sad, but I wasn’t at all surprised that they exist in many different water systems and that many, many people are getting exposed through their drinking water.”
—Jamie DeWitt

And Andrews and Naidenko’s study does not even fully capture Americans’ exposure to these chemicals because it only looks at two PFAS compounds and one source. “We're also being exposed to many more PFASs via the drinking water,” Wang says. The paper omitted other compounds because of a lack of widespread data, “but it means [the study offers] a conservative estimate of how we are being exposed to PFASs,” he adds. Higgins notes that people are also exposed to the compounds in substances besides drinking water, such as household products and food. “It's a much broader exposure question,” he says. “Those other sources of exposure should not be ignored.”

Andrews and Naidenko agree that the lack of data on other PFAS contamination is a problem. Other tests of drinking water from five systems in Massachusetts showed that levels of specific PFASs researchers looked for have risen over the past few decades. When scientists tested for PFASs as a group (to include compounds for which there are not much individual data), the increase was even larger. It remains unclear whether this trend holds true across the rest of the country. “That is really [because of] an absence of data—where the regulatory bodies have not kept up with the chemical industry, which has really moved away from PFOA and PFOS into hundreds of replacement compounds that are equally persistent and likely do contaminate a significant number of water systems across the country,” Andrews says.

The Environmental Protection Agency says it is working on the PFAS problem. “Aggressively addressing PFAS in drinking water continues to be an active and ongoing priority for the EPA,” an EPA spokesperson wrote to *Scientific American*. “The agency has taken significant steps to monitor for PFAS in drinking water and is following the process provided under the Safe Drinking Water Act to address these chemicals.”

Technologies to remove PFASs from drinking water exist on both household and municipal levels. Granular activated carbon filters and reverse osmosis are two options, but they are costly and high maintenance—and the burden falls on taxpayers. “PFASs are produced by companies, for which they receive a profit,” DeWitt says. “And then residents end up paying to clean up the pollution.” On top of that, PFASs that are removed from drinking water may simply end up elsewhere, such as in a landfill or river.

Some states have instituted or proposed limits on PFASs in drinking water, but experts say federal action is needed to tackle such a pervasive problem. President Joe Biden’s administration may finally address that need. His campaign’s environmental justice plan specifically called out forever chemicals. And the plan said that the president will “tackle PFAS pollution by designating PFAS as a hazardous substance, setting enforceable limits for PFAS in the Safe Drinking Water Act, prioritizing substitutes through procurement, and accelerating toxicity studies and research on PFAS.”

The new administration could carry out all of these goals unilaterally through executive action, without Congress’s cooperation. Some experts appear optimistic about this prospect. “I'm hopeful that the [new] administration will reempower the EPA so that it can actually create regulations to protect public health,” DeWitt says. “That is the agency’s charge—that is its mission.”

—Annie Sneed

The Pandemic Is Delaying Cancer Screenings and Detection

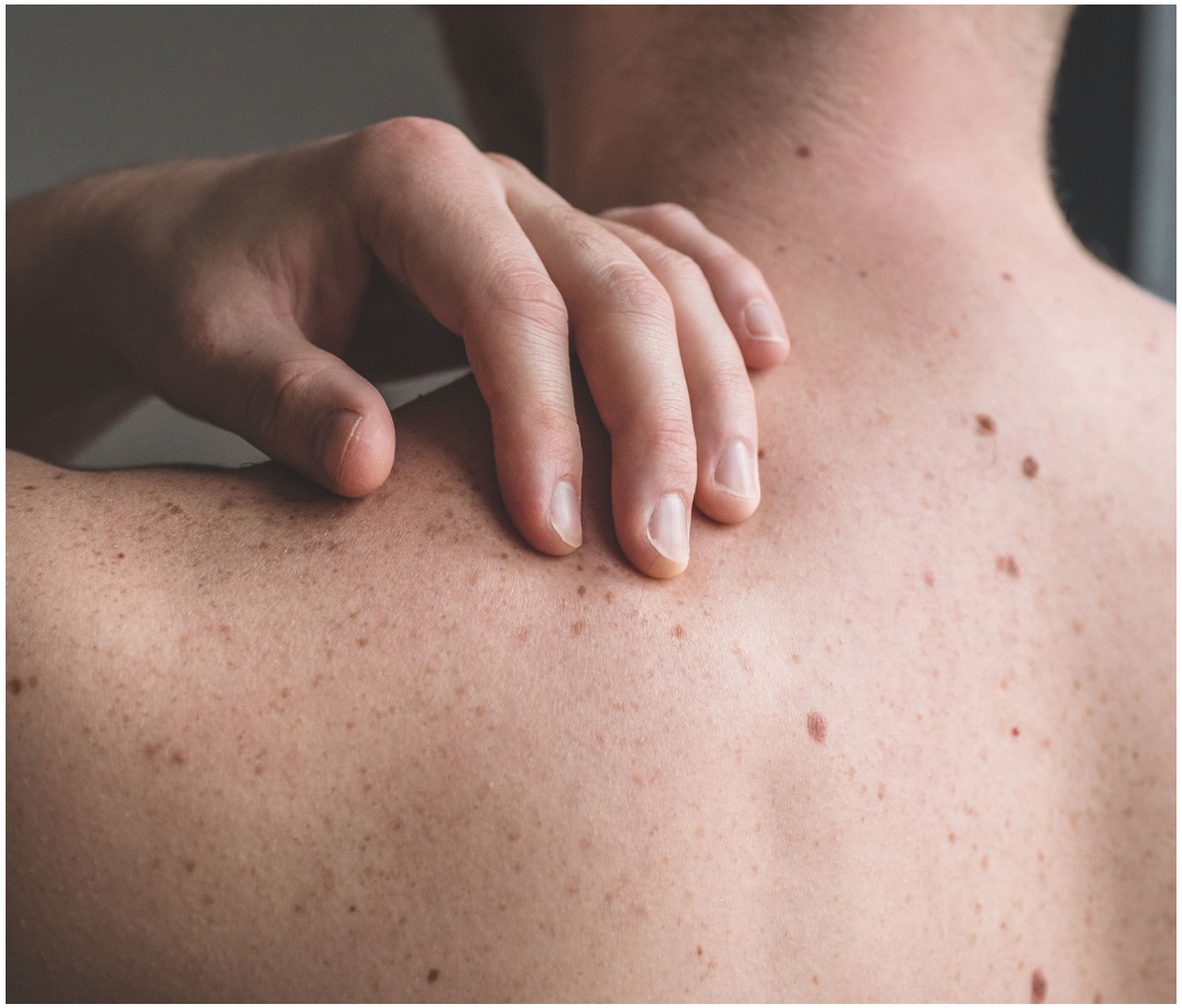
The missed checkups could result in later, more severe diagnoses down the line

After the World Health Organization declared COVID-19 a pandemic in March 2020, the scans that Josh Mailman relies on to keep tabs on his pancreatic neuroendocrine tumors were postponed three times until July. For Mailman—who says he had considered delaying the scans even longer to reduce unnecessary hospital visits during the pandemic—the results were shocking.

"Several of my tumors had doubled in size," says Mailman, who leads one of the largest U.S. support groups for patients with his type of cancer. Neuroendocrine tumors, with which he was diagnosed in 2007, usually grow slowly. Mailman says he felt fine prior to the scans, and his routine blood work had showed no cause for concern. "I spent three months in the dark," he says.

The rate of routine cancer screenings plummeted from January through April 2020, according to an analysis by the Epic Health Research Network. Screenings for breast and cervical cancers dropped by 94 percent. Colon cancer screenings were down by 86 percent. "We had a backlog of over 5,000 colonoscopies alone from the spring shutdown," says John Carethers, chair of internal medicine at the University of Michigan. Some people had to have their appointments deferred because of the continuing backlog, Carethers says. Others were reluctant to come in at all for fear of contracting COVID.

Screening rates began to rebound after the first wave of COVID but continue to fall short of 2019 levels, says William Cance, the American Cancer Society's chief medical and scientific officer. And while the pickup in screenings is a good sign overall, it does not reveal the full picture. "It doesn't tell us how many people who didn't get screened during the pandemic have actually come back to screening," says Monica Morrow, breast surgical service chief at Memorial Sloan Kettering Cancer Center in New York City.



ANASTASIA STIAHAILO *GETTY IMAGES*

Regular screening is associated with reduced mortality from various cancers, including colorectal and lung cancers. Missed screenings are especially worrisome because of the increasingly younger age of diagnosis observed in several cancers, such as colorectal cancer, in recent years, Cance says. It is also dangerous for cancers that tend to grow quickly, such as lung cancer. And screening is not the only way cancers are noticed. Some diagnoses may begin with a routine appointment with a primary care physician or with unrelated blood tests or scans. "The most common way a thyroid cancer is detected is

that somebody goes to their physician and gets a physical exam, and they stumble across a bump in the neck," says endocrinologist Bryan McIver, deputy physician in chief of the Moffitt Cancer Center in Florida. Skin cancers and cancers involving the lymph nodes are also often detected during a routine physical exam. Physician burnout and the financial strain on primary care practices as patient volumes drop during the pandemic may lead to the loss of tens of thousands of primary care physicians—and there was already a shortage before the pandemic began.

Alongside the decrease in screenings and biopsies, cancer diagnosis rates now appear to be in decline. A study in *JAMA Network Open* that compared weekly incidence reports from January through April 2020 of six common cancers, such as lung and colorectal cancer, to the same time period in 2019 found these rates declined significantly; the incidence of breast cancer dropped by up to 51.8 percent. In the U.K., another study found that new cancer diagnoses were down 65.2 percent in April 2020 compared with the same month the previous year. "I am seeing some patients who have had symptoms, who delayed going to see a doctor, and have had a delay in diagnosis of leukemia or other related disorders," says Mikkael Sekeres, chief of the division of hematology at the Sylvester Comprehensive Cancer Center at the University of Miami.

Doctors worry that missed detection opportunities may result in patients being diagnosed with more advanced, harder-to-treat stages of cancer in the future. "There's a hint that some patients are presenting later than they otherwise would have—with more advanced breast cancer, with more advanced prostate cancer," McIver says. "The iceberg still has to show itself in that regard."

The National Cancer Institute predicts 10,000 excess deaths from breast and colorectal cancers alone over the next decade in the U.S. Similarly, a *Lancet* study estimates that there may be an increase in cancer deaths as a result of diagnostic delays over the next five years, ranging from 4.8 percent for lung cancer to 16.6 percent for colorectal cancer. Delayed treatment, which can raise the risk of death, may be a contributing factor—an American Cancer Society Cancer Action Network survey of more than 2,000 cancer patients and survivors found that 32 percent of respondents actively undergoing cancer treatment reported delays in their care as of September 2020. An analysis of health-care service use from March through July 2020 found a decrease in some cancer procedures, including mastectomies.

Many experts agree that the pandemic's impact on cancer diagnoses, treatment and patient health will be felt for years to come. The delays will likely have a disproportionate effect on underserved communities, including Black, Native American and Hispanic people who are already bearing the brunt of COVID. Even before the pandemic, screening rates were lower and mortality rates were higher for some cancers in these communities because of barriers to health-care access such as a low income, being underinsured or uninsured, and food and housing insecurity. Soaring unemployment rates during the pandemic have only exacerbated these challenges.

"I think that if we see 10,000 excess [cancer] deaths over 10 years, the proportion of minority communities affected will be greater unless something is done," Carethers says.

At-home cancer-screening tools, such as fecal DNA tests for colorectal cancer, are being used in an attempt to bridge the gap. But the most accessible such test—fecal immunochemical testing—is not as effective as a colonoscopy in detecting disease. Moreover, there are no easy solutions if a patient tests positive and cannot access follow-up care, Carethers says.

As COVID cases have risen throughout the country once more, Sekeres says patient volumes at his cancer center have started to drop again. He and other doctors are encouraging people to avoid putting off routine screening, especially if they have risk factors such as a family history of cancer, and to seek medical care immediately if they are having symptoms.

As for Mailman, he says he is glad he did not delay his scans further. "I was very fortunate to take that scan, even if it was delayed three months," he says. "It kept me in a place where I could fight another day."

—Anna Goshua

Pathogen Discovered That Kills Endangered Chimps: Is It a Threat to Humans?

An Ebola outbreak and a few false leads slowed a 15-year search for bacteria that attack the nerves and gut

On a Friday evening in mid-January, Jackson, a five-year-old chimp living at Tacugama Chimpanzee Sanctuary in Sierra Leone, alarmed his keepers by ignoring his dinner. By Saturday, he was lethargic and having seizures. Jackson has improved since then—he is eating and seems stable, despite lingering diarrhea—but his survival is by no means guaranteed. "The disease is very much like that: you see ups and downs," says veterinarian Andrea Pizarro, general manager at Tacugama. "One day they're very good; the next, they're very bad."

Jackson has epizootic neurologic and gastroenteric syndrome (ENGS), a mysterious ailment that has killed 59 of the 60 Tacugama chimps that have come down with it since 2005.

Western chimpanzee (*Pan troglodytes verus*) at the Tacugama Chimpanzee Sanctuary in Sierra Leone.

After struggling to pinpoint the cause of the disease for years, scientists and veterinarians finally have a possible culprit: a newly discovered species of *Sarcina*, a type of bacteria commonly found in the environment and occasionally associated with gastrointestinal disease in humans. As the researchers report on February 3 in *Nature Communications*, the finding suggests that some *Sarcina* species may in fact be highly virulent but, until now, have not been recognized.

"Maybe there's this range of different *Sarcina* that look the same but have gained genetic properties that allow them to be more pathogenic," says lead study author Leah Owens, a veterinary and doctoral candidate at the University of Wisconsin–Madison. "That can have repercussions for human and animal health."

Tacugama is the only sanctuary in Sierra Leone for western chimpanzees, a critically endangered subspecies whose range once stretched across West Africa but is now confined to eight countries. Located eight miles southeast of Freetown, on the edge of the Western Area National Park, the accredited, award-winning sanctuary also carries out environmental education, ecotourism and community conservation projects. Ninety-nine chimps permanently reside at Tacugama today. Many of them were rescued as babies from the illegal wildlife trade.

Tacugama's chimps began coming down with ENGS in 2005, although it took years for veterinarians to realize that the animals they were losing had died of a common cause. The syndrome plays out differently in different individuals, with some showing neurological signs such as lack of coordination and seizures and others suffering gastrointestinal distress—or both. Some animals seem to recover from ENGS only to succumb weeks or months later, whereas others simply drop dead without any warning signs.

FABIAN VON POSER *ALAMY*

Tacugama's veterinarians pursued several red herrings, including a virus that causes neurological problems, for which they vaccinated every chimp at the sanctuary. They also undertook an exhaustive removal of a poisonous plant found in the chimps' enclosure. But cases kept coming. In 2016 the Pan African Sanctuary Alliance, an umbrella organization for the continent's primate sanctuaries, reached out to epidemiologist Tony Goldberg, Owens's adviser at the University of Wisconsin–Madison. Goldberg was immediately intrigued. "This is an unknown infectious disease that poses a serious risk to the health and survival of an endangered species, which happens to be our nearest relative," he says.

It took two and a half years to get permission to export the chimp samples to the U.S. (not the least because the Ebola outbreak was underway at the time) and to work out the logistics for safely shipping them. In the end, the Wisconsin researchers obtained tissue, blood, serum and fecal samples from 19 chimps that had died of the syndrome and 14 healthy ones. "One night I came into the lab, and we had this [shipment] full of liquid nitrogen," Owens says. "Tony was elated, like, 'Oh, my God, I've waiting years to look at these brains!'"

Owens, Goldberg and their colleagues performed a comprehensive analysis on the samples to characterize all of the viruses, bacteria and parasites present. Several of the samples "just had an insane number of reads for this one bacterium, like 90-plus percent," Owens says. Diagnostic sequencing and statistical analyses confirmed that the bacterium was not present in any of the healthy chimps, suggesting a link to ENGS.

By appearance, the microbe seemed to be *Sarcina ventriculi*, which looks a bit like a four-leaf clover and is ubiquitous in water and soil around the world. The species was first discovered in a 19th-century human patient who presented with vomiting, but it then largely disappeared from the scientific literature related to disease. Genome sequencing revealed, however, that the team had not found *S. ventriculi*, but a completely unknown *Sarcina* species, which the team named *Sarcina troglodytae.* "In all the decades knowing this bacterium exists, the medical community never appreciated that what they had been calling *S. ventriculi* might actually be a group of related bacteria," Goldberg says.

Chimps are not the only primates recently coming down with *Sarcina*. Since 2010 there has been a surge of cases of the bacterium turning up in human patients, often ones that have undergone bariatric surgery, mostly in the U.S. Clinicians have primarily diagnosed *S. ventriculi* based on appearance rather than genetics, however, making it impossible to say which species people are actually being infected by. But some human cases of *Sarcina* infection, including one fatal one, have presented with "eerily similar" effects to those seen in chimps, Owens says.

"The question is: Is this an emerging new pathogen that is different from the *Sarcina* we think we know?" she says. "Or is there something about the host that's changing, that's allowing them to get infected and sick from this?"

Owens and Goldberg hypothesize that there is a diversity of unrecognized *Sarcina* species, some of which are benign and some of which are opportunistic pathogens. The challenge now will be to untangle those different species, determine how the virulent ones are causing disease and tease out which environmental triggers inside or outside the body predispose certain primates to infection. Answering these questions could not only help protect an endangered species but people as well. As Owens says, "Chimps are basically us, genetically."

The findings also raise questions—and hope—for how to best go about treating Tacugama's primate residents for ENGS. "This study represents a starting point to guide further investigations in the unfortunate likelihood of future cases and offers ideas for tailoring treatment interventions," says Livia Patrono, a veterinarian and postdoctoral researcher in primate infectious disease at the Robert Koch Institute in Berlin, who was not involved in the work.

Already Tacugama's veterinarians are changing their approach to treatment. Jackson, unlike any infected chimps before, is being given probiotics and a special diet, in addition to targeted antibiotics. "Before, we were lost, trying to focus on everything," Pizarro says. "Now we know what we have to protect against."

—Rachel Nuwer

The Most Worrying Mutations in Five Emerging Coronavirus Variants

Here is a guide to novel versions of the COVID-causing virus—and genetic changes that can make them more contagious and evasive in the body

When the coronavirus SARS-CoV-2 burst on the world last winter, scientists knew it was bad. But they also thought it was stable. Coronaviruses do not mutate as readily as the viruses that cause the flu, hepatitis or AIDS, for instance—thanks in part to a molecular "proofreading" system that SARS-CoV-2 and its kin use to prevent damaging genetic errors when replicating.

Researchers were only partly right. The virus is indeed bad—but it is not so stable after all. SARS-CoV-2 has been acquiring minor random mutations ever since it jumped from animals to humans. These mutations can take the form of single-letter typos in the viral genetic code or dele-

Ambulance service paramedic Ronald Ramaselela leaves after assessing a COVID-19 patient in Lenasia, South Africa, on January 4, 2021. Currently suffering a second wave of infections, of which the majority are a new variant of the coronavirus, South Africa is the hardest-hit country on the African continent.

MICHELE SPATARI *GETTY IMAGES*

tions or insertions of longer stretches. When they occur, most mutations either kill the virus or cause no change in its structure or behavior.

But in recent months, several new variants of the original virus (also called the wild type) have been spotted that appear to cause major changes in the way the pathogen acts, including alterations to its contagiousness. These viral versions have seemingly popped up in rapid succession in different geographical regions, such as the U.K., South Africa and Brazil, and in some cases have outcompeted the existing variants. Although improved surveillance and sequencing efforts might partly explain why these variants are appearing now, some repetition in their patterns suggests the mutations are not random.

"What we're seeing is similar mutations arising in multiple places," says Adam Lauring, a virologist at the University of Michigan. "That's pretty suggestive that these mutations are doing something."

Specifically, they appear to help the virus transmit more readily and evade the immune system. In January researchers reported, for the first time, that antibodies from individuals with COVID did not completely neutralize a variant first identified in South Africa. A few people who recovered from the disease also appear to have been reinfected with the mutant virus.

Thus far vaccines made by Moderna and Pfizer seem to work against the new variants, although Moderna has begun developing a booster shot specific to new variants. Because these two vaccines are more than 90 percent effective, a slight drop in effectiveness would still make them worth using, experts say.

"I'm optimistic this won't compromise the [COVID vaccines], but obviously, it's something we've got to watch closely," Lauring says. In coming years, he adds, companies may need to retool these vaccines and administer updated versions, much in the same way that flu vaccines are revised every year. Most vaccines cause a much stronger immune reaction than a natural infection with a virus. And in clinical trials for its vaccine, Moderna found that the antibodies produced after vaccination may last longer than those naturally produced after SARS-CoV-2 infection.

Here are five of the most prominent variants, listed in the order that researchers first spotted them. This roster identifies where each variant was first seen and gives the technical name or names scientists use to identify it. (Naming variants has caused some confusion because different research teams employ different systems. This list uses one based on the ancestral lineage of each variant, but some variants still have more than one name.) The entries also highlight important mutations in each variant—denoted by letters and numbers that indicate their position in the sequence of the viral genome—and describe what scientists know or suspect about what those changes do.

SPAIN
Names: 20A.EU1, B.1.177
Notable mutation: A222V

The 20A.EU1 variant, first identified in Spain, contains a mutation called A222V on the viral spike protein. The spike is a component of SARS-CoV-2 that binds to a receptor on human cells called ACE2, and this attachment helps the virus get inside those cells and infect them. The spike protein is also the part of the pathogen that is targeted by human antibodies when they fight back against the infection. In laboratory tests, human antibodies were slightly less effective at neutralizing viruses with the A222V mutation. Over the course of several months, the 20A.EU1 variant became the dominant one in Europe. Epidemiologists never saw any evidence that it was more transmissible than the original, however. Researchers believe that when Europe began lifting travel restrictions last summer, the variant that was dominant in Spain spread across the continent.

U.K.
Names: 20I/501Y.V1, VOC202012/01, B.1.1.7
Notable mutation: N501Y

Scientists in the U.K. had been watching the B.1.1.7 variant for some time before announcing last December that it might be at least 50 percent more transmissible than the original form. That announcement was based on epidemiological data that showed the virus rapidly spreading throughout the nation. And it led to international travel bans and stronger lockdown measures in the U.K.

The B.1.1.7 variant contains 17

mutations, including several in the spike protein. One of them, N501Y, has been found to help the virus bind more tightly to the ACE2 cellular receptor. It is unclear, however, whether the variant's enhanced contagiousness comes from N501Y alone or also involves some combination of other spike protein mutations.

Despite initial concerns, there has been no real evidence that the variant is more infectious in children than the original, says University of Cambridge microbiologist Sharon Peacock, who is executive director of the COVID-19 Genomics UK (COG-UK) Consortium, a group that analyzes genetic changes to the virus. Both Pfizer and Moderna believe that their COVID-19 vaccines will still work against B.1.1.7. Recent data from the U.K. hint that the variant may be more lethal than the original, but the analyses are preliminary.

B.1.1.7 does stand out because it accumulated so many mutations, apparently all at once. Lauring and others suspect that these mutations may have arisen within one immunocompromised patient who was infected for a long time because that person was unable to fight off the virus. It is likely that only a few of these changes gave the variant an evolutionary advantage and allowed it to quickly spread around the U.K., says Scott Weaver, a microbiologist at the University of Texas Medical Branch at Galveston. The others were simply along for the ride.

SOUTH AFRICA
Names: 20H/501Y.V2, B.1.351
Notable mutations:
E484K, N501Y, K417N

The B.1.351 variant appeared around the same time as B.1.1.7, and it spread quickly in South Africa to become the dominant version in that country. Like its European counterpart, B.1.351 contains the N501Y mutation, although evidence seems to suggest the two variants arose independently. But scientists are more concerned about another mutation called E484K that appears in the South African version. The genetic change may help the virus evade the immune system and vaccines.

Using yeast cells, evolutionary and computational biologist Jesse Bloom of the Fred Hutchinson Cancer Research Center in Seattle and his lab created a series of spike proteins with almost all of the more than 3,800 possible protein component changes that could be driven by genetic mutations. Then the scientists tested how well or poorly human antibodies bound to each altered spike. They found that E484K—as well as similar mutations at that particular spot in the protein—made it as much as 10 times more difficult for antibodies to bind to the spike in some people. Bloom's lab also found that some antibody cocktails, such as one currently being tested by the drug and biotech companies Regeneron and Eli Lilly, may be less effective against mutations present in the B.1.351 variant.

In January researchers in South Africa released a preprint study (research that has not yet been peer-reviewed) showing that an antibody-containing serum from COVID patients was considerably less effective at neutralizing this variant. And in another preliminary preprint posted on January 26, scientists reported they put B.1.351 into serum taken from people who had been vaccinated with either the Pfizer or Moderna vaccine. They found antibodies in that serum showed reduced neutralizing activity against the mutant, compared with their activity against the original virus.

Antibodies in test tubes are not the same thing as vaccines in real people, however. Both vaccines produce so many antibodies that a drop in activity could still leave enough of them to neutralize the virus. The vaccines also stimulate other protective components of the immune system. Still, Moderna has begun work on a booster shot specific to new variants.

BRAZIL
Names: B.1.1.28, VOC202101/02, 20J/501Y.V3, P.1
Notable mutations: E484K, K417N/T, N501Y
Names: VUI202101/01, P.2
Notable mutation: E484K

In January researchers reported they had detected two new variants in Brazil, both descendants of a somewhat older common ancestor variant. Although they share mutations with other newly discovered versions, they appear to have arisen independently of those variants.

Of the two, researchers are currently more concerned about P.1. That variant contains more muta-

tions than P.2 (although both have E484K), and it has already been seen in Japan and other countries. Although it is possible that P.1 accumulated its mutations in an immunocompromised individual, genetics researcher Emma Hodcroft of the University of Bern in Switzerland says that it might be more difficult to pinpoint the time and place when this variant first arose because Brazil does not sequence nearly as many viral samples as the U.K.

Hodcroft points out that both Brazil and South Africa had large COVID outbreaks in 2020. With so many infected people creating antibodies against the virus, a version that could evade the immune system and reinfect a person who had recovered might have a strong advantage and then become more widespread in a population.

VIRAL SPREAD AND CHANGE

Although the seemingly sudden emergence of several spike protein variants is reason for concern, researchers say there is no evidence that the virus has changed in a fundamental way that lets it mutate more rapidly. What is most likely, Lauring says, is that the sheer number of COVID cases worldwide is allowing the virus numerous opportunities to change a little bit. Each infected person is, essentially, a chance for SARS-CoV-2 to reinvent itself. “Some of it is evolution, but a lot of it is epidemiology,” Lauring says. Overall, “the virus is getting better at being a virus.”

—Sara Reardon

COVID Can Cause Forgetfulness, Psychosis, Mania or a Stutter

The virus induces neurological symptoms that persist long after the pandemic ends

By Stephani Sutherland

GETTY IMAGES

Stephani Sutherland is a neuroscientist and science writer based in southern California.

PATRICK THORNTON, A 40-YEAR-OLD MATH TEACHER IN HOUSTON, TEX., relies on his voice to clearly communicate with his high school students. So when he began to feel he was recovering from COVID, he was relieved to get his voice back a month after losing it. Thornton got sick in mid-August 2020 and had symptoms typical of a moderate case: a sore throat, headaches, trouble breathing. By the end of September, "I was more or less counting myself as on the mend and healing," Thornton says. "But on September 25, I took a nap, and then my mom called." As the two spoke, Thornton's mother remarked that it was great that his voice was returning. Something was wrong, however.

"I realized that some of the words didn't feel right in my mouth, you know?" he says. They felt jumbled, stuck inside. Thornton had suddenly developed a severe stutter for the first time in his life. "I got my voice back, but it broke my mouth," he says. After relaying the story over several minutes, Thornton sighs heavily with exhaustion. The thought of going back to teaching with his stutter: "That was terrifying," he says.

In November, Thornton was still struggling with low energy, chest pain and headaches. And "sometimes my heart rate [would] just decide that we're being chased by a tiger out of nowhere," he adds. His stutter had only worsened by that time, Thornton says, and he worried that it reflected some more insidious condition in his brain, despite his doctors' insistence that the speech disruption was simply a product of stress.

A growing body of evidence warns that the legacy of the pandemic does not necessarily disappear when the novel coronavirus, or SARS-CoV-2, is cleared from the body. Among the millions of people who have survived respiratory complications from COVID-19, many still live with lingering symptoms in the wake of even a mild case of the disease. Neurological symptoms, ranging from fatigue to brain fog to loss of smell, persist after the virus is gone from the body.

An early survey of 153 COVID-19 patients in the U.K. and a more recent preprint study of people hospitalized with the disease in Italy both found that about a third had neurological symptoms of some kind. Other estimates have trended even higher. "There's a really wide spectrum of [neurological] manifestations of COVID," says Thomas Pollak, a neuropsychiatrist at King's College London and a co-author of the U.K. study. "Some are totally devastating, like stroke or encephalitis, and some are much more subtle." Increasingly common symptoms include fatigue and memory problems—and, at times, new cases of psychosis or mania.

Some neurological manifestations of post-COVID, such as stuttering, are more bizarre than others. But Houston's Thornton is not the only one afflicted. Soo-Eun Chang, a neuroscientist at the University of Michigan, is among the few researchers investigating stutter. "While stress and anxiety are not the cause of stutter, they do exacerbate it," Chang says, and that is true for Thornton. But she says the origins of the disorder lie in complex circuits of the brain that coordinate the millions of neuronal connections needed for human speech.

While most people develop this disruption of speech when they learn to talk, around age two, neurogenic stutter can arise after brain trauma, such as an injury. Chang says her colleagues in clinical practice have reported seeing an increase in cases of stuttering during the pandemic—mostly in people whose existing stutter worsened or whose childhood stutter returned.

Having the virus, she says, could lead to conditions that disrupt speech. "Speech is one of the more complex movement behaviors that humans perform," Chang says. "There are literally 100 muscles involved that have to coordinate on a millisecond time scale, so it's a significant feat. And it depends on a well-functioning brain."

COVID's inflammatory response could undermine the efficiency of these circuits. "An immune-mediated attack on synaptic connections could lead to a change in brain function," she says.

The idea that SARS-CoV-2 can get into the human brain is mainly supported by autopsy studies, such as one by Frank Heppner, a neuropathologist at Charité–University Medicine Berlin, and his colleagues. The researchers found evidence of the virus in specific areas of the brain, probably near the sites of entry. One could be the lining of the nasal passage, the olfactory mucosa, which is in close contact with neuronal cells that could provide a route to the brain. "We started at that region and then physically mapped [a pathway through] the regions up to the olfactory bulb and further to brain stem nuclei," Heppner says. The researchers found evidence of viral protein in those distant brain stem regions but not in other areas of the brain. "This told us, or made it likely, that the virus used the transmucosal route along the olfactory nerve as a port of entry," Heppner adds.

They also saw viral particles in trigeminal nerves, which are sensory nerves that enter the brain and transmit the pain of headache. Heppner says his team also discovered hints that the virus could get into the brain through blood vessels. But autopsies were undertaken in those with severe disease, and it is uncertain whether the virus gets into the brain in milder cases. For most people, the symptoms brought on by COVID are likely the result of immune system activity. "The virus gets cleared from the lungs, but the immune system is triggered and doing harmful things," Heppner says. "The same could be true for the central nervous system. It's a fair speculation. It could explain very well the long COVID symptoms like chronic fatigue and problems in concentration."

William Banks, who studies the blood-brain barrier (BBB) at the Department of Veterans Affairs Puget Sound Health Care System in Washington State and the University of Washington Medical School, says, "The virus doesn't have to get into the brain to muck up function. We know there's a big cytokine storm," meaning the release of inflammatory signals by immune cells in serious cases. Even mild cases provoke cytokine release, however. And Banks says it is well established that "cytokines can cross the blood-brain barrier and cause depressionlike symptoms." Researchers refer to those symptoms—including a loss of interest in life, an increased desire to rest and sleep, and cognitive impairments—as "sickness behavior," which often accompanies a flu or cold. Those symptoms could drag on if cytokines continue to be released after the infection has passed.

"We're a long way off from understanding exactly how these nebulous responses arise. But the general principle is that if you create a perturbation in the system or the brain, you'll affect its computational ability."
—Thomas Pollak

Yet another possibility is that the virus itself does not cross the BBB but that a viral protein, perhaps shed from a dying virus, might do so. Banks and his colleagues showed as much in a recent paper in *Nature Neuroscience*. They injected mice with S1, which makes up half of SARS-CoV-2's "spike" protein, and found that it readily crossed the BBB. Michelle Erickson, who works with Banks at the VA Puget Sound and the University of Washington Medical School, says that the work "adds, at least in mice, a defined route by which the virus can get into the brain, importantly, in the absence of inflammation," when the blood-brain barrier might be leaky. "We saw that spike can get into the intact BBB," she adds. "Often infiltration is almost entirely due to BBB disruption. But here it was only slightly disrupted, which was quite surprising to us."

The results hint that not only the S1 protein but potentially the virus itself could cross the BBB. A viral protein could cause damage by binding to proteins on neurons and other critical brain cells. "We know these binding proteins are very neurotoxic; they're stress-inducing," Banks says. And the presence of any viral material could "shoot off the immune system."

There is yet another possibility: the virus could lead the immune system to produce damaging autoantibodies. These proteins bind not only to the virus but to other proteins in the body as well, either disrupting their function directly or triggering an immune attack on cells. "COVID wreaks havoc with the immune system," says neuropsychiatrist Pollak. "There's a huge surge in various inflammatory mediators." Some early evidence suggests that anti-SARS-CoV-2 antibodies may react to tissues in the brain and body, he says, and that could possibly occur at neurons.

Autoantibodies are the culprit in a recently described neurological disease called anti-NMDA receptor encephalitis, which can cause fatigue, brain fog, and even psychosis and coma. The immune system proteins bind to NMDA receptors that are critical for neuronal signaling. "Binding to neuronal proteins tends to disrupt synaptic function, like in the case of anti-NMDA receptor antibodies," Pollak says. "That leads to signaling dysfunction, and information processing gets out of whack."

The autoantibody hypothesis still warrants further research. "It's probably the most speculative and the one we know the least about," Banks says. Fatigue, brain fog

and other symptoms probably arise from multiple different immune-mediated mechanisms. But researchers agree that synapses, where brain signals are passed from neuron to neuron, are probably disrupted. "We're a long way off from understanding exactly how these nebulous responses arise," Pollak says. "But the general principle is that if you create a perturbation in the system or the brain, you'll affect its computational ability."

Recent preprint work by Andrew Yang at the laboratory of Tony Wyss-Coray of Stanford University also hints that the brain undergoes widespread changes in the wake of COVID-19 that could contribute to neurological symptoms. Yang and his colleagues found altered patterns of genes switching on and off in cells from the brains of patients who had died of the disease. These differences were observed in neurons and other brain cells—glia and immune cells called microglia. The genetic activation patterns differed from those observed in people who died of the flu or nonviral causes.

Yang's team examined an area of the cortex and saw dramatic gene expression changes in neurons in a specific region called cortical layer 2/3. These neurons have been recently implicated as playing a pivotal role in the complex processing required for human thought, so disruption of their activity could lead to mental fuzziness.

The patterns of genetic changes the researchers saw in the cortex mirrored genetic pathways mapped out in mental illnesses such as schizophrenia and depression. In addition, Yang also found gene-expression changes in microglia, which clean up waste and eat dead cells in a process called phagocytosis. Microglia can consume, or phagocytose, neuron bodies and synapses, reshaping neural circuits if the cells are dying or even when they are under stress. Neurons generally do not regenerate, so cognitive function may be impaired.

It is not only neurological symptoms that afflict patients. More common mental illnesses are affecting people with COVID, too. A study published in the *Lancet Psychiatry* showed that having the disease led to greater risk for anxiety, depression and sleep disorders. Paul Harrison of the University of Oxford and his colleagues sifted through the electronic health records of nearly 70 million Americans and identified more than 62,000 people who had been diagnosed with COVID-19. In the three months following diagnosis, "we found that COVID was associated with roughly twice the incidence of common psychiatric diagnoses, compared with other health conditions," Harrison says.

Why COVID increased the risk for mental illness remains unclear. But Harrison says the virus itself is probably not directly responsible. He points to the psychological consequences of having a potentially fatal illness that could prevent you from returning from the hospital to your family. "There are all sorts of acute stresses associated with the diagnosis," he says. "I think those factors are going to be the most important explanation for the association we observed." Still, Harrison adds that the immune response provoked by the virus may have also had an effect on the brain that could have triggered psychiatric symptoms. He has a study underway to investigate the longer-term mental health effects of COVID-19, including symptoms such as brain fog and fatigue.

The legacy of COVID will undoubtedly persist. Although Thornton continued to struggle in December, his stutter and energy level had improved, and he had gone back to teaching. "The kids have been really good about it," he says. "It's been a rocky road, but there's light at the end."

Still, the lasting effects could mean not just bothersome symptoms for a few people but a public mental health crisis, Banks says. "It could ultimately turn out that—as horrible as the death rate is, with perhaps one in 1,000 Americans having died—in the end there, could be this legacy affecting up to one in 10," he adds. "And it's probably rooted in neuroimmunity." SA

Why COVID Vaccines Are Likely Safe for Pregnant People

The scantness of available data leaves the decision up to individuals and their doctors, although benefits can outweigh risks in some cases

By Mariana Lenharo

GETTY IMAGES

AS THE INITIAL PRIORITY GROUPS ARE BEING OFFERED A COVID-19 VACCINE IN THE U.S., one population in particular faces a difficult decision: Pregnant people who are health-care personnel or essential workers—categories that are eligible for the early phases of the vaccination program—"may choose to be vaccinated," according to the latest official guidance from the Centers for Disease Control and Prevention. The problem is that there are scant data available on the safety of COVID-19 vaccines in pregnant individuals. They were not included in the clinical trials, as has historically been the case with most vaccines and drugs.

"We've put pregnant women between a rock and a hard place," says Melanie Maykin, a maternal-fetal medicine fellow at the University of Hawaii at Manoa. She belongs to a committee at the Society for Maternal-Fetal Medicine that advocates for equitable care during pregnancy. In a recent study, Maykin and her colleagues noted that one evaluation had found that all nine global COVID-19 vaccine trials at the time listed pregnancy as an explicit exclusion criterion.

Epidemiologist David Schwartz of Augusta University, a specialist in global maternal health and obstetric, placental and perinatal pathology, says the tradition of not including those who are pregnant or lactating in vaccine development is partially attributable to the biological changes they undergo. "You're dealing with a tremendously altered human being," he says. "The maternal cardiovascular system is different, as well as the hemodynamics, the immunology and the pharmacodynamics." Also, vaccines and drugs can potentially pass through the placenta, and their effects on the fetus are very hard to assess. There are medical liability issues as well.

Pregnant people are often classified as a "vulnerable population," Maykin notes, and there is a strong historical reason for this. In the past, women of color and low-income women have, at times, been submitted to clinical trials without proper informed consent. Acts of exploitation included the initial birth-control pill tests, which used high doses that were found to have harmful side effects. "The solution is not to exclude [pregnant trial participants], however," Maykin says, "but rather to intentionally and justly include them, especially women of color and [those who are] low-income, as stakeholders in decisions around drug and vaccine development."

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WHAT WE KNOW SO FAR ABOUT SAFETY

Despite the reluctance to include pregnant individuals in clinical trials, this population still gets vaccines, and their safety has been closely monitored. "In general, vaccines seem quite safe in pregnant women," says Sonja Rasmussen, a professor in the departments of pediatrics and epidemiology at the University of Florida. Flu shots that do not involve a weakened live virus and the tetanus, diphtheria and whooping cough vaccine (called Tdap), for example, are not only considered safe but are actively recommended during pregnancy.

The latest review on the safety of the flu shot during pregnancy, conducted by the CDC, analyzed all of the 671 reports related to influenza vaccine and pregnancy in the Vaccine Adverse Event Reporting System (VAERS) from 2010 to 2016. Although conditions such as spontaneous abortion and major birth defects were reported, their prevalence in vaccinated pregnant individuals was similar to what occurs in the general population of pregnant people. This suggested that the flu shot was not associated with pregnancy problems. A recent systematic review focusing on the Tdap vaccine also concluded that when administered during second and third trimesters, it was not associated with any clinically significant harm to the fetus.

Although these findings are reassuring, a direct extrapolation to COVID-19 vaccines should be avoided. "The challenge is that we don't have a previous vaccine with the mRNA technology," says Linda Eckert, a professor of obstetrics and gynecology at the University of Washing-

ton. Both of the two vaccines that have been approved in the U.S.—which were developed by Pfizer-BioNTech and Moderna, respectively—use this technology.

One general guiding principle for vaccination during pregnancy is that live-virus vaccines are not recommended because of a hypothetical risk to the fetus, Maykin says. Neither the Pfizer-BioNTech or Moderna vaccine contains a live virus. They work by introducing mRNA, which is a set of instructions for our cells to build a piece of protein found on the surface of SARS-CoV-2, the virus that causes COVID-19. Our immune system then develops a response against that protein, producing antibodies that can fight the actual virus. "When you think of the biologic plausibility that this set of instructions, this mRNA, could cause any harm to the pregnant woman or the fetus, it's very unlikely because that mRNA gets degraded very quickly after the cell uses it to make the protein," Maykin says.

Experts also emphasize that the mRNA vaccines cannot alter human DNA. "One of the rumors that we're hearing is that this vaccine will mix with the fetal DNA, and that's not true," Eckert says. The mRNA never enters a cell's nucleus, which houses our DNA, and thus cannot affect the genetic material of the pregnant individual or fetus.

Animal experiments carried out by Moderna also suggested that its vaccine had no adverse effect on reproduction or on the development of fetuses in female rats. Pregnancy-related animal data for the Pfizer-BioNTech vaccine also seem to point toward similar conclusions.

The Johnson & Johnson COVID-19 vaccine, which was authorized by the FDA for emergency use at the end of February, is based on a distinct technology. It uses an adenovirus that has been genetically modified to be unable to cause illness as a vector. Like the Pfizer-BioNTech and Moderna vaccines, it was not tested in pregnant individuals.

Other vaccines developed by Johnson & Johnson that use the same adenovirus platform have been administered to a small number of people who happened to get pregnant around the time of the studies. But the data are not robust enough to draw any conclusions about its safety in this population. The company notes, however, that there is "no concerning pattern of [adverse events] in the pregnancies initiated around the time of vaccination."

"When you think of the biologic plausibility that this set of instructions, this mRNA, could cause any harm to the pregnant woman or the fetus, it's very unlikely because that mRNA gets degraded very quickly after the cell uses it to make the protein."

—Melanie Maykin

Animal studies done with an adenovirus vaccine against Ebola showed no maternal or fetal toxicity in female rabbits vaccinated during or immediately before pregnancy, according to Johnson & Johnson.

HOW COVID-19 IS AFFECTING PREGNANT PEOPLE

The absolute risk for developing severe COVID-19 during pregnancy is low. But compared with nonpregnant individuals, those who contract COVID-19 while pregnant are at increased risk of intensive care unit admission, invasive ventilation and death, according to U.S. data.

Additionally, several cases of SARS-CoV-2 infection have been reported in newborns. A recent systematic review analyzed 176 published cases, and in about 70 percent, the babies were probably infected after birth. In the other 30 percent, the virus is believed to have been transmitted by the pregnant individual, either during delivery or through the placenta. The latter scenario seems to be very rare, but cases have been documented.

Schwartz and his colleagues proposed a set of diagnostic criteria to determine which newborns were most likely to have been infected through the placenta before delivery. Together with a team of researchers from five countries, Schwartz identified a cohort of six live-born babies, as well as five cases of stillborn ones, who demonstrably acquired the infection when they were still in the womb. By analyzing these cases, the team identified two unusual placental abnormalities that seemed to occur in all the patients.

Although initial data from China in early 2020 seemed to suggest that the new coronavirus was not particularly harmful to pregnant people or their offspring, this perception changed as the disease spread and cases of severe pneumonia in pregnant people—as well as deaths among such individuals—were reported. "We realized that not only is this potentially life-threatening for a small percentage of pregnant women, but it seems to also be affecting the newborns," Schwartz says.

One of the first documented cases of SARS-CoV-2 infecting the placenta was registered at Yale New Haven Hospital in March 2020. Infectious disease specialist Shelli Farhadian, who is an assistant professor at the Yale School of Medicine, and her colleagues reported the case of a woman in the second trimester of pregnancy who was admitted to a hospital with COVID-19 symptoms. She developed severe preeclampsia and lost the fetus. After getting the patient's permission to check, the researchers found evidence of the virus in her placenta.

"She was one of the first cases, and we didn't know how common this would end up being," Farhadian says. Since

then, she and her team have systematically studied the placentas of COVID-19-positive patients admitted to the hospital at the time of delivery. In a new paper currently under review, they state that it is very rare to find evidence of SARS-CoV-2 infection of the placenta in full-term pregnancies. But people infected earlier in pregnancy have not been systematically studied, Farhadian notes.

PREGNANCY'S UNIQUE IMMUNOLOGIC STATE

For many years, it was believed that pregnancy was a state of immunologic weakness. The fact that pregnant individuals died more from diseases such as influenza was attributed to this state. More recently, it became clear that immunologic changes in pregnancy were much more complex than that. "They were not dying because they were immunosuppressed," says Gil Mor, scientific director of the C. S. Mott Center for Human Growth and Development at Wayne State University. "They were dying because their immune system was so strong and activated that they produced a massive inflammation that killed them."

Mor, who is an expert in the immunology of pregnancy, says there are several mechanisms to maintain the delicate balance between too much and too little inflammation during that state. If this balance is not maintained for any reason, the risk of severe COVID-19 symptoms rises.

The University of Florida's Rasmussen notes that it is still not clear if the increased risk to severe disease during pregnancy is related to an altered immune system or to other changes typical of the state, such as occasional breathing difficulty.

WEIGHING RISKS AND BENEFITS

The American College of Obstetricians and Gynecologists (ACOG) recently published a practice advisory recommending that COVID-19 vaccines should be available for pregnant or lactating individuals who are part of the priority groups defined by the CDC's Advisory Committee on Immunization Practices (ACIP). "What the ACOG really advocates for is for women to be able to make the decision for themselves and their fetus—that they have information so they can look at their particular circumstances and risks," says Eckert, who is ACOG's liaison on ACIP and helped to develop the organization's practice advisory.

"At this point, we are recommending that women talk with their health-care providers and weigh the risks and the benefits," Rasmussen says. For example, she adds, those who can work from home and avoid exposure may consider postponing vaccinations until after giving birth if their physician finds that appropriate. Frontline healthcare workers who are pregnant might consider getting the vaccine as soon as possible, however. Another variable to consider is the presence of other risk factors for COVID-19, such as cardiovascular or respiratory problems, which could weigh in favor of getting the vaccine promptly.

It is also unclear when it is best to be vaccinated during pregnancy. One known possible side effect of the authorized COVID-19 vaccines is fever, which is important to avoid during pregnancy—especially in the first trimester, when fever is associated with an increased risk of birth defects—Rasmussen says. Pregnant individuals vaccinated from the second trimester onward could potentially extend the protection to their developing child. In that stage, Mor says, the recipient is able to transfer antibodies through the placenta.

With so many variables and unknowns, experts acknowledge that this is a tough decision. "That's why I think it's important to have a trusted and reliable source of information, like your doctor, who is really staying abreast of the data and can help guide the decision-making," Maykin says. "Understandably, women might be hesitant." SA

Detecting Alzheimer's Gets Easier with a Simple Blood Test

New assays could reduce the need for costlier, more invasive brain scans and spinal fluid measures

By Esther Landhuis

GETTY IMAGES

Esther Landhuis is a freelance science journalist in the San Francisco Bay Area.

WHEN A PATIENT COMPLAINS of forgetfulness, a neurologist might not know immediately whether it results from normal aging, reduced blood flow to the brain—or, more ominously, Alzheimer's disease. For much of the past century, a definitive Alzheimer's diagnosis could only be made during an autopsy. Brain imaging and spinal fluid tests now make it possible to spot the disease in patients even before the initial symptoms appear. But these invasive tests are expensive and generally limited to research settings that are not part of routine care for the millions of people suffering from the most common neurodegenerative disorder.

An era in which an Alzheimer's diagnosis can begin in a doctor's office is now arriving. Advances in technologies to detect early signs of disease from a blood sample are helping doctors to identify the memory-robbing disorder more accurately and to screen participants more quickly for trials of potential treatments for the more than five million people in the U.S. afflicted with Alzheimer's. (Estimates predict that, by 2030, there will be 76 million people worldwide who will receive a diagnosis of Alzheimer's or other dementias.)

Last fall a blood test developed by C_2N Diagnostics in St. Louis, Mo., became available to most of the U.S. as a routine lab test—regulated under the CMS Clinical Laboratory Improvement Amendments (CLIA) program. It has also received a CE mark as a diagnostic medical device in the European Union—indicating it has met safety, health and environmental protection standards for the region.

"The development of a blood-based test for Alzheimer's disease is just phenomenal," says Michelle Mielke, a neuroscientist and epidemiologist at the Mayo Clinic. "The field has been thinking about this for a very long time. It's really been in the past couple of years that the possibility has come to fruition."

The C_2N test, called PrecivityAD, uses an analytic technique known as mass spectrometry to detect specific types of beta-amyloid, a protein fragment that is a pathological hallmark of disease. Beta-amyloid proteins accumulate and form plaques visible on brain scans two decades before a patient notices memory problems. As plaques build up in the brain, levels of beta-amyloid decline in the surrounding fluid. Such changes can be measured in spinal fluid samples—and now in blood, where beta-amyloid concentrations are significantly lower. PrecivityAD is the first blood test for Alzheimer's to be cleared for widespread use and one of a new generation of such assays that could enable early detection of the leading neurodegenerative disease—perhaps decades before the onset of the first symptoms.

PrecivityAD is meant for 60- to 91-year-olds with early signs of cognitive impairment. The prescribing physician ships patient blood samples for analysis at C_2N's lab and receives results within 10 business days. The results—a probability score that reflects the likelihood of an amyloid-positive brain scan—are calculated using a proprietary algorithm that incorporates the person's age with measurements of beta-amyloid and a protein called apolipoprotein E that is known to influence Alzheimer's disease risk.

Rather than serving as a stand-alone tool, the results are meant to enhance the accuracy of a clinical diagnosis by distinguishing Alzheimer's dementia from memory loss caused by other conditions. The test costs $1,250 and is not currently covered by insurance, although a financial assistance program can bring out-of-pocket costs down to between $25 and $400 for eligible patients, says C_2N's chief executive Joel Braunstein.

By comparison, beta-amyloid tests using positron-emission tomography (PET) brain imaging typically cost around $5,000 and are typically not covered by insurance, and those that sample cerebrospinal fluid (CSF) usually cost from $800 to $1,000. Compared with these more invasive and burdensome procedures, the ease and lower cost of blood tests open up many exciting possibilities for clinical use and therapeutic development," says Adam Boxer, a neurologist at the University of California, San Francisco. "Blood tests can be collected from people

repeatedly in remote locations or in their homes." No drugs have yet been approved that change the course of Alzheimer's. But readily available early tests could improve treatment by letting patients take measures to stay healthy, affording them an opportunity to plan for an uncertain future and participate in clinical trials.

From a preventive standpoint, blood tests could "help identify who's at risk," Mielke says. Testing could also be used to screen potential participants for experimental drugs. In some past trials of beta-amyloid-reducing treatments, 15 to 30 percent of patients who met clinical criteria for Alzheimer's turned out not to have brain amyloid. Nowadays trials often require participants to show evidence of disease pathology through PET scans or CSF measures. Prescreening with a cheap blood test could halve the number of PET scans needed to enroll volunteers, according to a new study published on January 22 in the journal *Brain*.

This would lower the cost of trials, which means "more potential treatments can be tested, and that increases the chances of finding a cure," says Elisabeth Thijssen, a researcher studying blood biomarkers for Alzheimer's at Amsterdam University Medical Centers in the Netherlands. Blood tests would be particularly helpful in identifying patients for trials of potential drugs that could be most effective long before the first symptom of cognitive decline.

Looking for beta-amyloid is not the only option. Some researchers believe other disease markers—for example, certain forms of the protein tau—could prove more promising when incorporated in blood tests for Alzheimer's. Beta-amyloid levels start to drop very early in the disease process and then reach a plateau, whereas tau markers go up later and continue to rise. That observation suggests amyloid tests could work better for early detection, whereas tau levels are more meaningful at later stages of the disease, when someone is on the verge of decline or already symptomatic, says Oskar Hansson, a neurologist at Lund University in Sweden. Last year Thijssen and Hansson published separate studies showing that tau blood tests could distinguish Alzheimer's from other neurodegenerative diseases nearly as well as CSF measurements and PET scans. Quanterix, a company in Billerica, Mass., has developed an immunoassay that detects amyloid and tau in conjunction with other neurological markers and inflammatory proteins. So far these tests are not available outside of research settings.

"We researchers are superenthusiastic" about these tests, Thijssen says. Most studies have been conducted in extensively studied groups of patients in neurology clinics, however. "Now we have to make the step into the real world," she says. When a new patient comes in with memory complaints, "is a blood test going to help physicians make a proper diagnosis?"

Patients in other settings may have other ailments that could affect the accuracy of assays. Some medical conditions can influence the levels of blood proteins, possibly skewing test results. "If somebody has chronic kidney disease, that can affect the clearance of proteins," Mielke says. "Individuals with a high body mass index tend to have higher blood volume, so that could reduce protein levels."

U.C.S.F. neurologist Gil Rabinovici agrees that "all these markers need to be validated in more diverse and generalizable cohorts." He is helping to lead a new study that will test blood assays against amyloid PET scans in 5,000 patients recruited at 350 clinical sites—with an emphasis on patients from Black and Latinx populations, which are historically underrepresented in dementia research. SA

Volunteers spray disinfectant in the city of Handan in China's Hebei province on January 23, 2021. The number of coronavirus patients bounced up recently in northern China.

Why Are We Still Deep Cleaning Surfaces for COVID?

The coronavirus behind the pandemic can linger on doorknobs and other surfaces, but these aren't a major source of infection

By Dyani Lewis

GETTY IMAGES

Dyani Lewis is a freelance science journalist in Melbourne, Australia.

WHEN EMANUEL GOLDMAN WENT TO HIS LOCAL NEW JERSEY supermarket in March, 2020, he didn't take any chances. Reports of COVID-19 cases were popping up across the U.S., so he donned gloves to avoid contaminated surfaces and wore a mask to prevent him inhaling tiny virus-laden droplets from fellow shoppers. Neither gloves nor masks were recommended at the time.

Then, at the end of March, a laboratory study showed that the coronavirus SARS-CoV-2 can persist on plastic and stainless steel for days. That triggered startling headlines and a slew of advice on how to decontaminate everything from doorknobs to groceries. It also seemed to confirm guidance issued by the World Health Organization (WHO) in February that the virus that causes COVID-19 can spread through contaminated surfaces, known as fomites.

By May, the WHO and health agencies around the world were recommending that people in ordinary community settings—houses, buses, churches, schools and shops—should clean and disinfect surfaces, especially those that are frequently touched. Disinfectant factories worked around the clock to keep up with heavy demand.

But Goldman, a microbiologist at Rutgers New Jersey Medical School in Newark, decided to take a closer look at the evidence around fomites. What he found was that there was little to support the idea that SARS-CoV-2 passes from one person to another through contaminated surfaces. He wrote a pointed commentary for the *Lancet Infectious Diseases* in July, arguing that surfaces presented relatively little risk of transmitting the virus. His conviction has only strengthened since then, and Goldman has long since abandoned the gloves.

Many others reached similar conclusions. In fact, the U.S. Centers for Disease Control and Prevention clarified its guidance about surface transmission last May, stating that this route is "not thought to be the main way the virus spreads." It now states that transmission through surfaces is "not thought to be a common way that COVID-19 spreads."

As evidence has accumulated over the course of the pandemic, scientific understanding about the virus has changed. Studies and investigations of outbreaks all point to the majority of transmissions occurring as a result of infected people spewing out large droplets and small particles called aerosols when they cough, talk or breathe. These can be directly inhaled by people close by. Surface transmission, though possible, is not thought to be a significant risk.

But it's easier to clean surfaces than improve ventilation—especially in the winter—and consumers have come to expect disinfection protocols. That means that governments, companies and individuals continue to invest vast amounts of time and money in deep-cleaning efforts. By the end of 2020, global sales of surface disinfectant totaled $4.5 billion, a jump of more than 30 percent over the previous year. The New York Metropolitan Transit Authority (MTA), which oversees subways and buses and lost billions of dollars in passenger revenue in 2020, spent $484 million last year in its response to COVID-19, including enhanced cleaning and sanitization, according to a spokesperson.

Part of the problem is that specialists can't rule out the possibility of fomite transmission, and the guidance from many health agencies about how to deal with surfaces has been unclear as the science has changed. Last November, Chinese authorities introduced guidelines requiring disinfection of imported frozen-food packages. And the CDC directs people to a comprehensive list of agents that kill SARS-C0V-2 and says: "Frequent disinfection of surfaces and objects touched by multiple people is important."

Experts say that it makes sense to recommend hand washing, but some researchers are pushing back against the focus on surfaces. In December, engineer Linsey Marr of Virginia Tech co-wrote an opinion article for the *Washington Post* imploring people to ease up on cleaning efforts. "It's become clear that transmission by inhalation of aerosols—the microscopic droplets—is an important if not dominant mode of transmission," says Marr, who

studies airborne disease transmission. Excessive attention on making surfaces pristine takes up limited time and resources that would be better spent on ventilation or the decontamination of the air that people breathe, she says.

VIRUS RNA CAN MISLEAD

The focus on fomites—rather than aerosols—emerged at the very beginning of the coronavirus outbreak because of what people knew about other infectious diseases. In hospitals, pathogens such as methicillin-resistant *Staphylococcus aureus*, respiratory syncytial virus and norovirus can cling to bed rails or hitch a ride from one person to the next on a doctor's stethoscope. So as soon as people started falling ill from the coronavirus, researchers began swabbing hospital rooms and quarantine facilities for places the virus could be lurking. And it seemed to be everywhere.

In medical facilities, personal items such as reading glasses and water bottles tested positive for traces of viral RNA—the main way that researchers identify viral contamination. So, too, did bed rails and air vents. In quarantined households, wash basins and showers harboured the RNA, and in restaurants, wooden chopsticks were found to be contaminated. And early studies suggested that contamination could linger for weeks. Seventeen days after the *Diamond Princess* cruise ship was vacated, scientists found viral RNA on surfaces in cabins of the 712 passengers and crew members who tested positive for COVID-19.

But contamination with viral RNA is not necessarily cause for alarm, Goldman says. "The viral RNA is the equivalent of the corpse of the virus," he says. "It's not infectious."

To address that part of the equation, researchers began testing whether coronavirus samples left for days on various surfaces could infect lab-grown cells. One study last April found that the virus remained infectious on hard surfaces such as plastic and stainless steel for six days; on bank notes, it lasted for three days; and on surgical masks, at least seven days. A later study announced that viable virus was present on skin for up to four days, but on clothes it survived for less than eight hours. And others found infectious virus on library books bound in natural and synthetic leather after eight days.

Person disinfecting table surface.

GETTY IMAGES

Although these types of experiment demonstrate that the coronavirus can survive on surfaces, this doesn't mean that people are catching it from surfaces such as doorknobs. Goldman and others caution against reading too much into virus-survival studies, because most don't test conditions that exist outside the lab. "They were experiments that started out with humongous amounts of virus, nothing that you would encounter in the real world," he says. Other tests have used mock saliva and controlled conditions such as humidity and temperature, all of which widen the gulf between experimental and real-world conditions, Goldman says.

Only a handful of studies have looked for viable virus outside the lab. Tal Brosh-Nissimov, who heads the infectious diseases unit at the Assuta Ashdod University Hospital in Israel, and his colleagues swabbed personal items and furniture in hospital isolation units and rooms at a quarantine hotel. Half of the samples from two hos-

pitals and more than one third of samples from the quarantine hotel were positive for viral RNA. But none of the viral material was actually able to infect cells, the researchers reported.

Indeed, scientists have struggled to isolate viable virus from any environmental samples, not just fomites. In the only study that has succeeded, researchers grew virus particles from hospital air samples collected at least two meters from a person with COVID-19.

Nevertheless, investigators warn against drawing absolute conclusions. "Just because viability can't be shown, it doesn't mean that there wasn't contagious virus there at some point," says epidemiologist Ben Cowling of the University of Hong Kong.

Human exposure studies of other pathogens provide additional clues about fomite transmission of respiratory viruses. In 1987 researchers at the University of Wisconsin–Madison put healthy volunteers in a room to play cards with people infected with a common cold rhinovirus. When the healthy volunteers had their arms restrained to stop them touching their faces and prevent them transferring the virus from contaminated surfaces, half became infected. A similar number of volunteers who were unrestrained also became infected. In a separate experiment, cards and poker chips that had been handled and coughed on by sick volunteers were taken to a separate room, where healthy volunteers were instructed to play poker while rubbing their eyes and noses. The only possible mode of transmission was through the contaminated cards and chips; none became infected. The combination of experiments provided strong evidence that rhinoviruses spread through the air. But such studies are considered unethical for SARS-CoV-2 because it can kill.

Although it is probably rare, Cowling says, transmission through surfaces can't be ruled out. "It just doesn't seem to happen that much, as far as we can tell."

Estimates of transmission based on levels of viral RNA persisting in the environment seem to bear this out. From April to June 2020, environmental engineer Amy Pickering, then at Tufts University, and her colleagues took weekly swabs of indoor and outdoor surfaces around a town in Massachusetts. On the basis of the levels of RNA contamination and how often people touched surfaces such as doorknobs and buttons at pedestrian crossings, the team estimated that the risk of infection from touching a contaminated surface is less than five in 10,000—lower than estimates for SARS-CoV-2 infection through aerosols and lower than surface-transmission risk for influenza or norovirus.

"Fomite transmission is possible, but it just seems to be rare. A lot of things have to fall into place for that transmission to happen."

—Amy Pickering

"Fomite transmission is possible, but it just seems to be rare," says Pickering, who is now at the University of California, Berkeley. "A lot of things have to fall into place for that transmission to happen."

That might explain why a global comparison of government interventions to control the pandemic in its early months found that cleaning and disinfection of shared surfaces ranked one of the least effective at reducing transmission. Social distancing and travel restrictions, including lockdowns, worked the best.

MESSY DATA

That leaves researchers sorting through messy epidemiological data about how the virus spreads. Hundreds of studies of COVID-19 transmission have been published since the pandemic began, yet there is thought to be only one that reports transmission through a contaminated surface, by what it termed the snot-oral route. According to the report, a person with COVID-19 in China blew his nose with his hand and then pressed a button in his apartment building elevator. A second resident in the building then touched the same button and flossed with a toothpick immediately after, thereby transferring the virus from button to mouth. But without genome sequences of the viruses infecting each person, transmission through another unknown person couldn't be ruled out.

In one other case, eight people in China are thought to have been infected after stepping in sewage containing the virus on the street and then walking the contaminant into their homes.

Despite the rarity of published examples of fomite transmission, Chinese authorities require that imported frozen food be disinfected. The change in guidelines followed a report, which has not been released in detail, that a worker at a frozen-food business in the northern port city of Tianjin became infected after handling contaminated packaging of frozen pork imported from Germany. But the WHO and other experts have disputed claims that people can be infected through the food chain in this manner.

Cowling says that more detailed investigations are needed, carefully tracking who infects whom and what surfaces and spaces they shared around the time of infection. "What we really, really value is epidemiological investigations of transmission patterns, whether it's in households or workplaces or elsewhere," he says. "I don't think we've been doing enough of that."

"You never want to say, 'Oh, don't do that,' because it can happen. And you know, we should follow the precautionary principle."

—Linsey Marr

THE GREATEST THREAT

Armed with a year's worth of data about coronavirus cases, researchers say one fact is clear. It's people, not surfaces, that should be the main cause for concern. Evidence from superspreading events, where numerous people are infected at once, usually in a crowded indoor space, clearly point to airborne transmission, Marr says. "You have to make up some really convoluted scenarios in order to explain superspreading events with contaminated surfaces," she says.

Hand washing is crucial, Marr says, because surface transmission cannot be ruled out. But it is more important to improve ventilation systems or to install air purifiers than to sterilize surfaces, she notes. "If we've already paid attention to the air and we have some extra time and resources, then, yes, wiping down those high-touch surfaces could be helpful," she says.

Households can also ease up, Pickering says. Quarantining groceries or disinfecting every surface is going too far. "That's a lot of work, and it also is probably not reducing your exposure that much," she says. Instead reasonable hand hygiene, as well as wearing a mask and social distancing to reduce exposure from close contacts, is a better place to focus efforts.

The WHO updated its guidance on October 20, 2020, saying that the virus can spread "after infected people sneeze, cough on, or touch surfaces, or objects, such as tables, doorknobs and handrails." A WHO spokesperson told *Nature* that "there is limited evidence of transmission through fomites. Nevertheless, fomite transmission is considered a possible mode of transmission, given consistent finding of environmental contamination, with positive identification of SARS-CoV-2 RNA in the vicinity of people infected with SARS-CoV-2." The WHO adds that "disinfection practices are important to reduce the potential for COVID-19 virus contamination."

The CDC did not respond to *Nature*'s queries about inconsistencies in its statements about the risks posed by fomites.

The conundrum facing health authorities, Marr says, is that definitively ruling out surface transmission is hard. Authorities can be reluctant to tell people not to be cautious. "You never want to say, 'Oh, don't do that,' because it can happen. And you know, we should follow the precautionary principle," she says.

Despite the evolving evidence, the public might have grown to expect extra levels of sanitization after the early months of the pandemic. When the New York MTA surveyed passengers in late September and early October of 2020, three quarters said that cleaning and disinfecting made them feel safe when using transport.

Goldman continues to wear a cloth mask when he leaves home, but when it comes to the possibility of catching the coronavirus from a contaminated surface, he doesn't take any special precautions. "One of the ways we protect ourselves is by washing our hands," he says, "and that applies pandemic or no pandemic." SA

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Carolyn Barber has been an emergency department physician for 25 years. She is co-founder of the homeless work program Wheels of Change and author of many articles and a new book, *Runaway Medicine: What You Don't Know May Kill You*, which was recently named an Amazon #1 Hot New Release in Health Care Administration.

PUBLIC HEALTH

The Problem of "Long Haul" COVID

More and more patients are dealing with major symptoms that last for months

GETTY IMAGES

It was just a couple of months into the pandemic when patients in online support groups began describing the phenomenon. In some emergency departments, they said, their complaints were largely being dismissed—or at the very least diminished—by health-care professionals. The patients felt they were not being heard or perhaps even were outright disbelieved.

The common thread through these comments was a basic one. Each of the patients had already been infected with COVID-19 and presumably had recovered, yet each was still dealing with symptoms of the disease—sometimes vague, sometimes nonspecific—that simply would not go away. Physicians and nurses, already overloaded with emergent cases of the virus, were baffled, often searching for other, more benign explanations for what they were being told.

We now have a term for those patients—and the truth is, "long hauler" only begins to describe the COVID-related ordeals they are enduring. Of all the facets of the virus we dealt with in 2020, this one may ultimately prove the most difficult to recognize, much less combat.

Long-haul COVID patients carry their symptoms well beyond what we've come to understand as a "normal" course of recovery. It can last for weeks. For some long haulers, it has been months—and counting. And to the consternation of physicians and nurses on the front lines, the symptoms of these patients often present as so varied and relatively common that they defy a solid COVID-related diagnosis.

If a patient comes to the emergency department complaining of dizziness, forgetfulness and

headache, for example, is that long-haul COVID or something else entirely? How about fatigue? A persistent cough? Muscle aches and insomnia? Relapsing fevers?

With little to go on and lacking clinical guidance, some of us in the emergency department have instructed our patients to go home, get more rest, "try to relax." We've offered reassurances that everything would be okay with more time, checked off the final diagnosis box for something like anxiety or chronic fatigue on our computers, and moved on to see our next patients.

But there's a growing body of evidence to suggest that a surprising number of people are, in fact, COVID long haulers and that hospital emergency departments and clinics may be dealing with them for months and months to come.

"Over the past few months evidence has mounted about the serious long-term effects of COVID-19," said World Health Organization director-general Tedros Adhanom at an international long-COVID forum last December. At the same event, Danny Altmann, an immunologist at London's Imperial College, said that his "guesstimate is that we probably have way more than five million people on the planet with long COVID." The worldwide percentages of infection suggest that many of those people are living and suffering in the U.S.

Long COVID is neither well defined nor well understood, in part because the research base is still in its infancy. The term "long hauler" is broadly used to characterize individuals whose symptoms persist or develop outside the initial viral infection,

"From my perspective, it appears that post-COVID symptoms tend to be more common, severe, and longer-lasting than other viral illnesses, such as influenza."
—Timothy Hendrich

but the duration and pathogenesis are unknown. Late sequelae have been described even in young, healthy people who had mild initial infection. And symptoms are often described by long haulers as being relapsing and remitting in nature—they improve, only to be struck back down again.

This reporting of this entire phenomenon has been inside out. In fact, this may be one of the first syndromes that evolved from patients' accounts on social media. As the early weeks and months passed, patients joined Facebook groups, Twitter feeds, and other online support groups—the Body Politic COVID-19 Support Group is one—to share stories of the myriad long-hauler symptoms that they were experiencing post-COVID, bringing visibility to the problem.

The persistent effects were wide-ranging and included cognitive issues such as "brain fog" and memory or attention problems, shortness of breath, a racing heart, nausea, diarrhea, intermittent spiking fevers—on and on. "A lot of us have the experience of really actually not knowing whether we would wake up in the morning," said event participant Margaret O'Hara, co-founder of Long Covid Support Group, which has 31,000 members. Members even began collecting data about themselves, organizing their own Patient-Led Research for Covid-19 group.

What has emerged from this self-reporting is the clear realization that long COVID is very real, that the chronic health manifestations can be quite debilitating, that the syndrome may affect a significant number of individuals, and that much more research and care provision are urgently needed.

"From my perspective, it appears that post-COVID symptoms tend to be more common, severe, and longer-lasting than other viral illnesses, such as influenza," says Timothy Hendrich, a viral immunologist and infectious disease expert at University of California, San Francisco.

The cause? It's not clear. A post–intensive care syndrome is well recognized whereby patients, following discharge after a critical illness, can suffer from impairments of thinking, mental health and physical function that can last up to a year. The catch here is that long-haul COVID patients experiencing similar impairments have not all been hospitalized or critically ill.

This may be the result of an immune-inflammatory response gone amok or perhaps of ongoing viral activity. Says Hendrich, "The etiologies are almost certainly multifactorial but may involve overzealous immune responses, cardiopulmonary or systemic inflammation, vascular inflammation or clotting disorders, and direct damage from viral

replication during acute illness." We currently have no proven treatments for these types of long-term post-COVID symptoms, he adds.

One challenge is getting a real picture of how many people are affected. In a recent study in the journal *Clinical Microbiology and Infection*, a two-month follow-up of 150 adults with only mild to moderate COVID cases found that two thirds of them were still experiencing symptoms, most commonly shortness of breath, loss of smell and taste, and/or fatigue. Another study by Italian researchers, covering 143 COVID patients who had been discharged from the hospital, found that only about one in eight was completely free of symptoms 60 days from the beginnings of the illness.

One of the largest surveys so far, the King's College London study, had four million users in the U.K. enter their ongoing symptoms on a smartphone app. The researchers reported that around 10 percent of patients had persistent symptoms for one month, with 1.5 to 2 percent having sustained symptoms at three months. As Hendrich suggests, this idea of "how many" is a moving target that will require more study and analysis.

King's College researchers, reviewing their data from the COVID Symptom Study, identified patterns that suggested long COVID was twice as common in women as men, and the median age was 45. A nonpeer-reviewed study of approximately 4,100 people from the same data set found that older people, women, and those with more than five symptoms during their first week of illness were more likely to develop long COVID.

Early clinical studies have shown that COVID patients may experience complications such as myocarditis (inflammation of the heart), abnormal heart rhythms and other cardiac sequelae weeks after contracting the virus. These conditions may help explain why some long haulers experience shortness of breath, chest pain or their heart racing. One nonpeer-reviewed study, involving 139 health-care workers who developed coronavirus infection and recovered, found that about 10 weeks after their initial symptoms, 37 percent of them were diagnosed with myocarditis or myopericarditis—and fewer than half of those had showed symptoms at the time of their scans.

Persistent shortness of breath—not being able to climb up a few flights of stairs, for example, or being unable to complete usual exertional activities without getting winded—are complaints repeatedly seen on long-COVID forum sites. Small studies have found persistent lung findings such as fibrosis (a form of lung scarring), perhaps explaining these symptoms. A retrospective multicenter study published in the *Lancet* of 55 recovered noncritical patients found that more than 60 percent of patients had persistent symptoms three months after discharge, and just over 70 percent had abnormal findings on their lung CT scans. A quarter had demonstrable reductions in lung function.

Long haulers also have commonly described neurologic symptoms that include dizziness, headache, loss of smell or taste, and so on. Carlos del Rio of the Emory University School of Medicine wrote in a review that although stroke is not commonly reported acutely with COVID, encephalitis (inflammation of the brain), seizures and brain fog have been described several months after the initial infection.

While there is much to learn, one study found that the most serious neurologic manifestations occurred in patients who experienced severe COVID infections, were older and had comorbidities. Anthony Fauci has expressed concern that some long haulers may develop myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which has been linked to another coronavirus, severe acute respiratory syndrome (SARS). Several viruses, including SARS-CoV-1, HIV, Middle East respiratory syndrome (MERS), polio and the chicken pox virus, have been known to trigger delayed neurological sequelae.

Researchers are carefully monitoring mental health outcomes, too. Unquestionably, the longer-term psychosocial effects this virus is exacting on COVID survivors have yet to be fully elucidated. Anxiety, hopelessness, depression, even post-traumatic stress disorder—especially in health-care workers or patients following ICU experiences—have all been reported and need further study.

Amid all this there lies some good news. First, physicians and our medical communities now are much more aware of long-hauler syndrome. Post-COVID clinics now exist, offering a much needed multidisciplinary and integrated approach. The Neuro COVID-19 Clinic at

Northwestern Memorial Hospital, for example, has been very busy, according to its director, Igor Koralnik.

Research studies may well shine a brighter light on the symptoms of long-COVID patients, affording us a better understanding of who gets this condition and why and suggesting possible interventions. Yet we're still in early stages: the National Institutes of Health ClinicalTrials.gov Web site shows fewer than a dozen post-COVID trials currently planned in the U.S., and scientists reported from the Long COVID forum that there are only 45 long-COVID projects underway worldwide, out of some 5,000-plus total COVID research projects.

It's a situation we should be prepared to face. In del Rio's words, "hundreds of thousands, if not millions" of individuals in the U.S. may wind up dealing with a multitude of adverse physical and mental health effects over the long term—and some anecdotal accounts of children experiencing long-haul symptoms are especially worrisome.

This may not be the aspect of COVID we thought we'd be seeing, but it's the aspect we are going to be dealing with—and for some time. As Tim Spector of King's College wrote in the foreword of a report for the Tony Blair Institute for Global Change, "This is the other side of Covid." Long after we've implemented strategies for dealing with the first wave of infection, our physicians are going to be seeing the many waves that follow.

Thomas Hall is senior principal technical adviser for malaria at Management Sciences for Health, a nonprofit global health organization.

PUBLIC HEALTH

A New Strain of Drug-Resistant Malaria Has Sprung Up in Africa

Here's how we fight back

YANICK FOLLY *GETTY IMAGES*

Ever since the deadly parasite responsible for malaria was discovered in the late 19th century, science and global health experts have been waging a vigorous Sisyphean battle against the disease it causes. Humans have brought an arsenal of tools—nets, rapid tests, medication—to bear against the mosquito-borne parasite, which cannily mutates to become resistant to drug treatments. We're holding our own: global malaria deaths declined to 409,000 in 2019, compared with 585,000 in 2010, and a number of countries have eliminated it altogether or are on the verge of doing so.

Yet more than 90 percent of the deaths occur in Africa, and there is a threat that could set progress back again. Researchers in Rwanda identified a strain of the malaria parasite *Plasmodium falciparum* with mutations on a gene known as *K13* that enable resistance to artemisinin, the foundation of artemisinin-based combination therapies (ACTs), the most commonly used malaria treatments. While ACTs still work, a weakened treatment regimen could lead to more deaths on the continent, an increased spread of resistance itself, and loss of confidence in malaria treatment.

We must act now to increase surveillance and monitoring for signs of new *K13* mutations, even as we battle the COVID-19 pandemic. In addition

to basic tactics such as increasing people's access to insecticide-treated mosquito nets, here's what can help make a difference:

Ensure that providers and patients use drugs effectively. When providers don't prescribe treatments correctly or their patients don't take the complete course as prescribed, it contributes to the emergence of drug-resistant malaria parasites. Governments and global health programs need to reinforce effective, safe prescribing and appropriate use of ACTs. For example, largely through USAID-funded initiatives, Management Sciences for Health supports malaria case management in Benin, Madagascar, Malawi and Nigeria. The program trains, mentors and evaluates health-care providers on the use of national malaria treatment guidelines.

Take action today to maximize the longevity of ACTs. The battle to delay artemisinin drug resistance must be fought on two fronts. The first is to support the use of quality-assured medicines at the correct dosage and to continually monitor their therapeutic efficacy against any emerging signs of resistance. The second is to support national malaria programs to adopt and deploy more than one artemisinin-based treatment, such as second-line or even multiple first-line therapies along with the addition of single low-dose primaquine to help block the transmission of resistant parasites, in line with WHO guidance. Strategies such as adding a third drug to an ACT—forming a triple ACT, or TACT—are also being investigated. Finally, we need to acknowledge that the sun may be setting on today's drugs. It may be a long sunset, but we need to be ready for tomorrow.

Develop the next generation of treatments. Medicines for Malaria Venture (MMV), a not-for-profit research and development organization, and its research and pharma partners have developed the largest portfolio of antimalarials in history. The most advanced new antimalarial medicine targeting parasites showing resistance to current drugs is in development with Swiss health-care company Novartis. It is now in clinical trials and is aimed at treating children as young as six months, as malaria kills more children under five than any other age group. National malaria-control programs must be ready to incorporate this potential new medicine in their budgets and treatment guidelines when it becomes available.

Expand lab-testing capacity. Improved surveillance to track the spread of resistant plasmodia is critical to maintaining progress, including using molecular and genomic techniques. But many sub-Saharan African countries do not yet have the equipment, personnel, funding or infrastructure to efficiently handle sequencing for malaria. Here, too, investors and collaborators must strengthen and build additional capacity. The National Institutes of Health and the Wellcome Trust have established the Human Heredity and Health in Africa (H3Africa) initiative to build capacity on the continent, as is the U.S. President's Malaria Initiative–supported Antimalarial Resistance Monitoring in Africa Network, which also supports collaborative efforts across the continent. The Africa CDC and the African Academy of Sciences have provided funding. Much more is still needed for sufficient lab capacity.

Develop a cross-border action plan with neighboring countries. Now that resistant parasites have been documented in Rwanda, they may be carried by travelers across borders or may already be in other African countries. National malaria-control programs and WHO regional and country offices need to reinforce intercountry collaboration, sharing information as well as educating health-care providers and communities about the implications of the mutation. Pharmaceutical regulatory agencies should continue to monitor and enforce quality standards to prevent and tackle substandard and falsified medicines, which greatly contribute to drug resistance. The West African Health Organization; Southern African Development Community; and East, Central and Southern African Health Community should work together to align efforts.

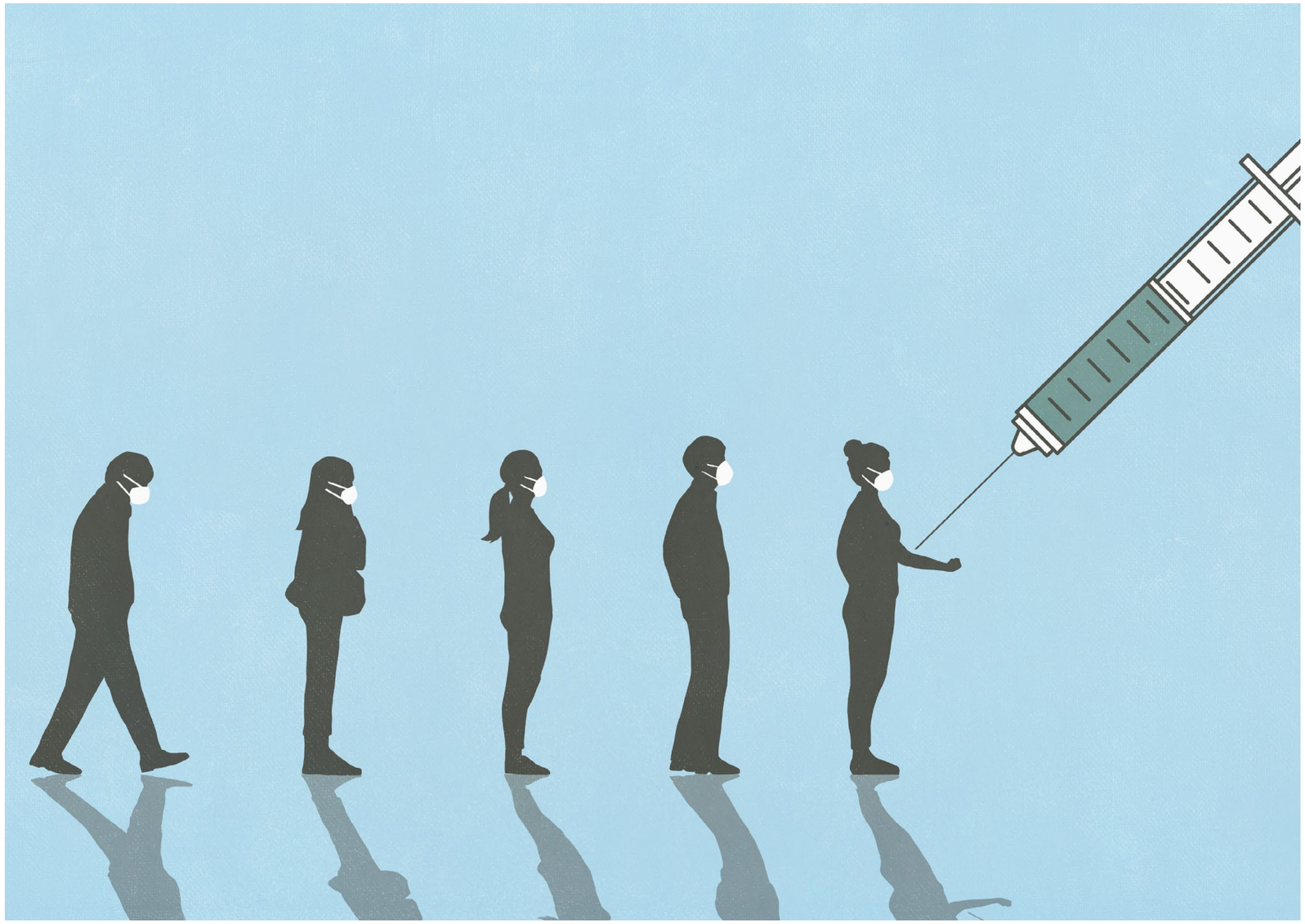
Southeast Asia had already seen this mutation as of 2013 and has been holding it at bay with careful use of drugs that work where they are most needed. We can outsmart this. We must bring our collective human ingenuity and determination to ensure that the continent bearing the world's greatest burden of malaria stays one step ahead of the emerging threat of this dangerous mutant parasite.

Steven W. Thrasher is a professor at Northwestern University in the Medill School of Journalism and the Institute of Sexual and Gender Minority Health and Wellbeing. He is author of the forthcoming book *The Viral Underclass: How Racism, Ableism and Capitalism Plague Humans on the Margins* (Celadon Books and Macmillan Publishing).

POLICY & ETHICS

If You've Been Working from Home, Please Wait for Your Vaccine

You can't ethically go ahead of the very people who made it possible for you to do so—at great personal risk



MALTA MUELLER *GETTY IMAGES*

To me, it's simple.

If you, like me, are not medically compromised and have been working from home over the past year while drawing your full salary, you have two options.

You can sit patiently until some institution calls you to get vaccinated.

Or you can proactively organize with other people to make sure your government is distributing vaccines equitably to people who need them the most, especially those who don't have many advocates—such as the millions of people who are living in congregate care settings, in prisons or in tent cities in the U.S. and the billions of people living in poor countries around the world.

But if you, like me, have been working from home and drawing your full salary in the pandemic, you cannot be trying to game the Internet to get vaccinated before the (disproportionately Black and brown) postal carriers, hospital orderlies, cooks, food delivery people, Amazon package drivers, bus drivers, nurses, day care workers, doctors, grocery store shelf stockers, order fulfilment warehouse specialists, cashiers, people who've lost their jobs at your workplace while

you've kept yours, people who never had a job or a home while you had both—and anyone else you may have banged a pot for at sunset in the early days of COVID.

In other words, if you've been working from home, you can't ethically be line jumping ahead of the very people who made it possible for you to work from home, at great personal risk.

At some level, "Prioritization vs speed is a false choice that ignores that we're expecting to transition from vaccine scarcity to abundance over the course of the year (in the US, very different scenarios in different countries, some have abundance now, others have nothing w/ no end in sight)," as Lindsay Wiley, director of the Health Law and Policy Program at American University Washington College of Law, wrote on Twitter. But those of us who have enjoyed the considerable prophylactic protection of working from home need to allow the prophylactic protection of a vaccine to first go to those who did not get to work from home—and especially for those who don't work in traditional jobs because they are disabled, unhoused, elderly or locked up.

As Wiley wrote, "Prioritization is critical to reducing hospitalizations & deaths ASAP. The difference b/w getting vaxxed today vs. summer is massive for, eg, people w/high-risk conditions whose work/family members' work is high exposure. The rest of us can/should wait a few more months."

In my own circles, my frustration has been less with people trying to get vaccines because they can (and before those vaccines expire and go to waste, which is an understandable position). My anger more is at the U.S. government (and the corporate forces that own it), which have created a neoliberal free-for-all in vaccine distribution. This has largely instructed people in most states that they have to find the government to get vaccinated instead of the government coming to them.

It is unconscionable that a pandemic that is slaughtering people who are elderly, severely disabled, experiencing homelessness and/or incarcerated also requires them to come to the government by way of Internet sign-up, QR codes and even two-factor cell-phone authentication.

This is an ableist trap. How can the government expect people who are illiterate, computer-illiterate, living on the streets and/or perhaps unable to use a computer because of their advanced age supposed to navigate such hoops?

In matters of law and war, the government is willing to come to us. When I turned 18, the U.S. government found me and told me (under threat of prosecution) to sign up for the Selective Service, so that I could be drafted in the event of a war. If any of us do not pay our taxes, you can be sure the U.S. government will find us, garnishing our wages if necessary—and if we break the law, police from our local government will arrest many of us quite quickly.

Yet when it comes to voting or vaccination, the government makes us go to it—and with votes and vaccines both, that decision generates predictably racist and ableist disparities.

There needs to be less collective thinking along the line of "I better get mine" and more proactive collective planning to make sure people who need vaccines the most desperately are getting them. Also, we need to interrogate how "I just showed up and got one before it expired" isn't an option for many who can't "just show up" (for example, people who are immunocompromised or are literally locked up in congregate living facilities or prisons). As my friend, epidemiologist Gregg Gonsalves of the Yale School of Public Health, wrote in the Atlantic: "In the United States, we have far too much practice in ignoring the ethical dilemmas staring us in the face."

As it has been for a year, COVID is an opportunity to rethink our deepest ethical assumptions.

I work primarily in two domains: as a journalist, among people who tell stories of the society, and as a professor of media and LGBTQ health, among a lot of people who study infectious diseases. My fellow journalists are narrating the vaccine story too much as a story of tech; but, to be fair, this has largely been because our federal and state governments have ceded the rollout to neoliberal tech patches largely run by private entities and not enacted the robust state approach that has been successful with past vaccination campaigns (without the aid of computers, let alone the Internet).

When 330 million people are all left to scramble for a vaccine through private tech platforms, all the inequities of tech exacerbate existing disparities to create an ever more distinct viral divide between who is being harmed by SARS-CoV-2 and who isn't. A vaccine is a technology

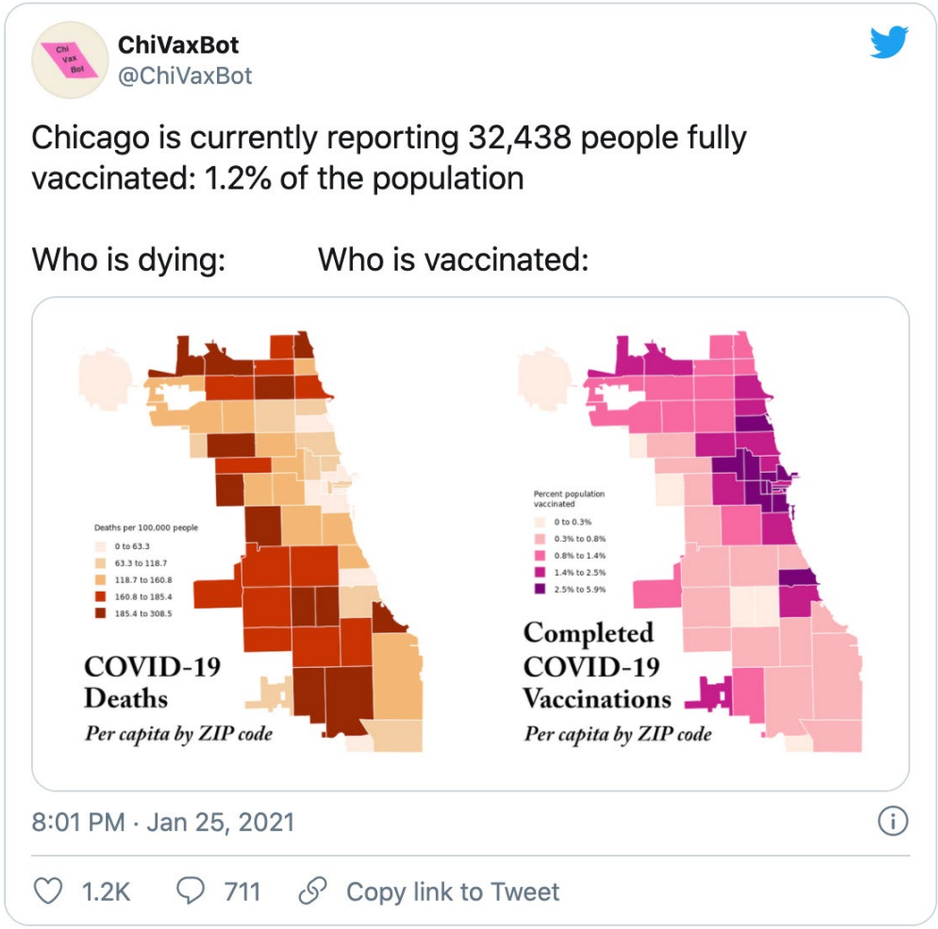
itself, and as I wrote last December, absent an actively antiracist, anticapitalist approach, vaccines are likely to exacerbate existing disparities, as medical interventions alone have before.

But access to the vaccine rollout itself is also technical in nature—and, as it's always been whenever it's trotted out as a panacea to address social injustice, tech has been an abysmal failure here.

Mastering tech has given an unfair advantage not to those who are most vulnerable but to those with the skills (or the grandchildren with the skills) most suited to using an app. Mastering tech has let white New Yorkers go to the heavily Latin neighborhood of Washington Heights—whose residents were very hard hit by COVID—to get shots, as though they're trawling for tacos they read about in Time Out. Tech is being used to encourage Americans to travel to other countries to get vaccinated, even when the people living there have not been. The allure of tech led the city of Philadelphia to largely turn over vaccination distribution to a start-up with a 22-year-old CEO, with predictably disastrous results.

Such a disaster was made possible, in part, by journalists who've irresponsibly written up start-up CEOs for years as mythic heroes who can solve complex social problems with their technical "disruptions."

On the academic side of my life, I have noticed that by far, the largest group of people I see getting vaccinated in my social media feeds are other professors who are also working from home. This is somewhat expected, given whom I know. But they—or rather, I should say, we—are highly educated people adept at navigating complex technical systems. People like us have kept our jobs even as custodians and food workers on our campuses have lost theirs. A recent map of Chicago, where I work (at least I did when campus life was a thing), that tracks who is dying of COVID and who is getting vaccinated against it alarmingly showed almost inverse populations.



All of this makes me afraid that, because the rules have been catered to us, those of us least likely to get COVID are the most likely to get vaccinations first (and to even feel like we deserve it because we figured it out), when we should be getting them last because we've had other forms of protection.

Of course, there are professors (and other people who've been working from home) who have compromised immune systems or live with people who are working in public-facing jobs who need vaccines ASAP. But I've also heard professors justifying their desire for vaccines because they have conferences planned they want to get to in 2021.

Listen, I love an academic conference as much as the next person. (Actually that's a bald-faced lie—I hate them, always have, and perhaps the one good thing about the pandemic has been that it's forced the more democratized sharing of academic knowledge on the Internet, keeping it from being hoarded by those who can afford to share it with four other people and 396 empty chairs in a Marriott conference room that could easily seat 400.) But "getting back to normal" is no reason for us to rush to the front of the line—especially when there are K–12 educators who have been doing face-to-face work, as well as truly essential college educators, such as cooks and dorm maintenance workers.

And those who have lost jobs at our very institutions need vaccines the most. Now that they are more likely to be living with other essen-

tial workers or facing eviction (which is its own COVID driver), or both, they need more—not less—organized protection when they are not formally attached to an institution.

And who will advocate for them?

We can.

If you have the time and technical ability to spend 12 hours online trying to get a shot for yourself while working from home, you can spend 12 hours organizing with others to make sure those most vulnerable can get theirs first or—even better—organizing to force the Joe "I believe in science" Biden's administration to make the government come to us, so that professionals are paid to schedule all of us and find us so that no one has to spend 12 hours trying to get an appointment.

As Lindsay Wiley wrote, a "better approach" during this time "when doses are scarce is to scale up mobile efforts to send doses (& jabbers) directly to hot-spot workplaces & residences & vax everyone on-site who's willing. That's what the federal nursing home program was supposed to do, but it lacked funding & oversight." In its wake, a "survival of the fittest" mentality has taken over, as people with means scramble individually online, with systems that encourage people to treat appointments like they're vying for Beyoncé tickets on StubHub.

Meanwhile there has been a fantastic success story in West Virginia, premised with a very different model. Despite being named at times the poorest state in the nation, West Virginia has had the best vaccine rollout. The state achieved this not through a neoliberal free-for-all, but because it was the only state to shun the outsourcing of nursing home vaccination to CVS and Walgreens. Instead the state used local health departments and small pharmacies with ties to communities.

As Wiley observed, "WV nursing home program (they opted out of the fed disaster) provides a model for scaling up mobile vax teams to target scarce doses. Local health departments play matchmaker between employers/housing authorities/etc and pharmacy teams and provide financing, logistics and oversight."

"Vaccinations and medicine should be distributed equitably, but the neediest are seldom at the front of the line," as Gonsalves's *Atlantic* piece noted. Indeed, as disability activist and author Alice Wong has been writing, California's "switch to an age-based vaccination plan" that greatly widened who is trying to get it also "de-prioritizes high-risk people under 65" like her, which is leaving disabled people more vulnerable. If there were less austerity in production and more abundance and even anarchy (horizontal planning about how we can collectively protect one another through mutual aid) with vaccination, 330 million people wouldn't need to be pitted against one another.

"Vaccinations and medicine should be distributed equitably, but the neediest are seldom at the front of the line."

—Gregg Gonsalves

Hopefully the Biden administration will ramp up production as promised, and patents will not be used as an excuse not to be manufacturing vaccines en masse around the world for all earthlings. In the meantime, those of us who have been working from home and are not especially vulnerable need not be passive about people who really need them. As the *Washington Post* reported, only one of the world's poorest 29 countries has gotten any COVID vaccine; meanwhile young Americans working from home are trying to get vaccines to go to conferences and Burning Man!

As Gonsalves reminded me, South African AIDS activist Zackie Achmat risked his own life and famously refused to take HIV meds until everyone who needed them had access.

Everyone doesn't need to be so extreme. But we needn't be passive about accepting an "I got mine" mentality when billions might go without, either—and if those with means don't demand access for those who don't, the viral underclass will only grow larger.

Still, if you really want to be passive as someone who works from home about everything, that can be as simple as letting someone else who might need a vaccine more go first—and quietly waiting around.

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PUBLIC HEALTH

Another Way to Protect against COVID beyond Masking and Social Distancing

Boosting indoor humidity in winter can hinder transmission of the virus

The first reference to the seasonality of infectious respiratory disease was recorded around 400 B.C., when the renowned ancient Greek physician Hippocrates wrote the earliest account of a winter epidemic of such an illness. Ever since, we have pondered the impact of seasonal change on respiratory disease prevalence. And rightly so, because even before COVID-19, respiratory diseases were having a profound impact on global health. In the U.S. alone, the Centers for Disease Control and Prevention reports that influenza has caused up to 61,000 deaths annually since 2010—and the World Health Organization suggests that, globally, 650,000 deaths are associated with seasonal flu each year.

GETTY IMAGES

So far scientists have identified at least nine distinct viruses that can cause respiratory tract infection and that demonstrate seasonality in their outbreak pattern in temperate regions. Of these, three viruses—influenza viruses, human coronaviruses and human respiratory syncytial virus (RSV)—clearly peak during winter months.

One obvious possibility is that seasonal changes in climate directly cause a spike in respiratory illness. The reality may be much more complex, however. In fact, the answer to seasonal occurrence of disease is more likely to be linked to our indoor environments rather than those outside.

Today most of us are likely to spend up to 90 percent of our time indoors. This is a significant issue because our buildings have become more sophisticated over the past century or so with the introduction of central heating systems and the development of increasingly airtight, insulated building shells. The result is that we are more and more disconnected from daily and seasonal outdoor climatic fluctuations, especially in winter.

Research, including our own, is beginning to illustrate that there is a relation between the aerial transmission of viruses and temperature and humidity, which is impacted by both indoor and outdoor environments.

It is obvious that in winter, indoor heating causes a difference between indoor and outdoor temperature. But what we are increasingly coming to understand is that by heating our buildings we are causing a reduction in the level of indoor relative humidity (RH), which has a significant impact on disease spread. For example, measurements of humidities in 40 residential apartments in New York City and in six high-quality commercial buildings in the Midwest showed that indoor RH dropped to below 24 percent in the winter. The evidence suggests, in other words, that when cold outdoor air with little moisture to start with is brought indoors and warmed to a temperature range of 20 to 24 degrees Celsius (68 to 75 degrees Fahrenheit), indoor relative humidity plummets.

This comparatively moisture-free air provides a clear path for dispersal of airborne particles of viruses such as SARS-CoV-2, the pathogen that causes COVID-19. The SARS-CoV-2 virus survives better at low temperatures and low humidity. Estimated virus half-life was more than 24 hours at 10 degrees C (50 degrees F) and 40 percent relative humidity but only 90 minutes at 27 degrees C (80 degrees F) and 65 percent relative humidity. Our own research indicates that dry air also reduces the ability of our body's cilia—hairlike projections on cells lining airways—to remove viral particles and prevent them from reaching the lungs. Finally, the immune system's ability to respond to pathogens is suppressed in drier environments. Indeed, a study conducted in New South Wales, Australia, demonstrates an inverse relation between relative humidity and transmission of SARS-CoV-2.

As the COVID-19 pandemic continues, this research could play a vital role in how we manage and counter the disease. Until we have enough vaccines to cover a large portion of human populations, we must keep practicing social distancing, mask wearing and avoiding crowding indoors. In addition to these measures, we can increase indoor humidity to combat the spread and prevent more severe disease from COVID-19.

This is why I and others specializing in immunobiology and infection control are urging the scientific community and others to support our petition, which calls on the WHO to urgently put the link between indoor air humidity and the transmission of viruses, including SARS-CoV-2, at the front of the global health debate. We are requesting that the WHO produce clear guidelines on the minimum lower limit of air humidity in buildings. We recommend maintaining relative humidity between 40 to 60 percent to maximize the benefits of humidity but not the drawbacks of too much humidity that promote mold growth.

We hope that through this move we will reduce the spread of SARS-CoV-2 and other airborne viruses and safeguard residents, students, patients and employees—which is crucial for protecting public buildings, such as nursing homes, hospitals, schools and offices. This is not just about getting America, and the world, back to work. It is also to offer protection for our health-care workers. While of course, there is a complex web of influences at play, we now know enough about indoor relative humidity's impact on disease for it to be viewed as a significant factor. Indoor air control is the next frontier to improve human health and reduce transmission of various types of viruses, including SARS-CoV-2.

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