SCIENTIFIC AMERICAN
Health & Medicine

June–July 2022

Plus:

CAN DOCTORS FIGHT GUN VIOLENCE?

EFFECTS OF LEGALIZING MARIJUANA

ANTI-HEALTH TRANS LAWS

Safe Pandemic Living

HOW TO ASSESS RISK AND MAKE THE BEST CHOICES IN THE TIME OF COVID

WITH COVERAGE FROM nature

Liz Tormes

How to Live In the COVID Age

We seem to have entered a rather murky phase of the pandemic here in the United States. Most states have lifted indoor mask mandates, restrictions on the size of public gatherings, and vaccination requirements to enter businesses. Shows, concerts and awards ceremonies have recommenced. But make no mistake, this global scourge is by no means over, despite a seeming return to normal. In the United States, we passed one million COVID deaths in the second week of May. Virus caseloads remain high in many places, and potentially contracting the disease is especially risky for those over 50 or the unvaccinated. Knowing how to live in a time like this feels a bit confusing, given these conflicting facts (and with the less-than-helpful guidance from our own Centers for Disease Control and Prevention). In this issue, writer Devabhaktuni Srikrishna spoke to a slew of public health experts about how to judge the risk of whether to participate in different activities in the COVID age, and their advice is sound and comforting (see "How to Make Smart Decisions about COVID Risk-Benefit").

Every day we learn more about the novel coronavirus and the sickness it causes, from what recovery looks like (see "Even Mild COVID Can Increase the Risk of Heart Problems") to how we might better diagnose and treat the disease (see "A Deluge of New Drugs for COVID"). Each stage of this pandemic has had its own set of challenges. The key is to keep calm, stay informed and do your best.

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Health & Medicine

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Chris Gash

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How to assess risk and make the best choices in the time of COVID

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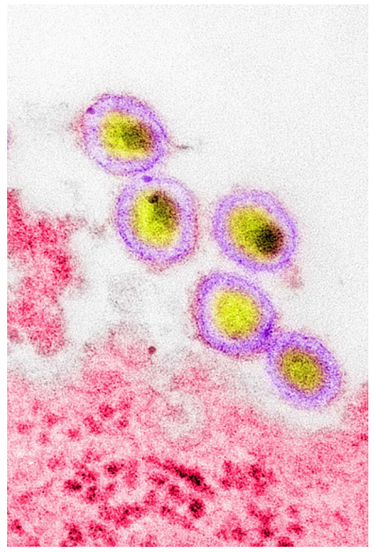

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Jeff J Mitchell/Getty Images

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Stephen Zenner/SOPA Images/LightRocket via Getty Images

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COVID Vaccines plus Infection Can Lead to Months of Immunity

New research counters high-profile claims that people who had COVID don't benefit from vaccination

Even people who have had COVID-19 receive long-lasting benefits from a full course of vaccination, according to three recent studies. What's more, one of the studies found that the "hybrid" immunity caused by vaccination and infection is long-lasting, conferring highly effective protection against symptomatic disease for at least six to eight months after vaccination.

The data were collected before the Omicron variant emerged, casting some doubt on the studies' relevance today. But if the findings hold up, they could inform vaccination schemes and vaccine passports, which some countries require for entry to places such as restaurants. The work also counters high-profile claims that people who have had COVID don't benefit from vaccination.

Just such a claim helped to launch some of the research. Brazilian president Jair Bolsonaro "said that he already had COVID-19, and for this reason, it is not necessary to take a vaccination," says Julio Croda, an infectious disease doctor and epidemiologist at the Oswaldo Cruz Foundation in Rio de Janeiro. Croda and his colleagues drew on Brazilian vaccination and infection databases to test such assertions.

The researchers found that between February 2020 and November 2021, people who had previously been infected with SARS-CoV-2 and then received one vaccine dose—made by either

Apu Gomes/AFP via Getty Images

Pfizer-BioNTech, Oxford-AstraZeneca, SinoVac or Johnson & Johnson—avoided as many as 45 percent of the COVID cases that the group would have been expected to contract without vaccination. Full courses of two-dose vaccines prevented as many as 65 percent of expected infections and more than 80 percent of expected cases of severe COVID. "The big message is this: you need to have a full vaccination scheme for COVID-19," Croda says.

"The big message is this: you need to have a full vaccination scheme for COVID-19."

—Julio Croda

"IMMUNITY" PASSPORTS?

Some authorities consider previous infections when deciding who should have entry to public places such as concerts and restaurants, but others consider only vaccination status. Peter Nordström, an epidemiologist at Umeå University in Sweden, says this dichotomy prompted him and his colleagues to perform another of the studies. Using records collected by the Public Health Agency of Sweden between March 2020 and October 2021, the researchers showed that Swedish residents who had been infected with SARS-CoV-2 had a 95 percent reduction in their risk of contracting COVID compared with people who had no immunity—and protection grew over the three months following infection and lasted until at least 20 months after infection. One dose of vaccine reduced the risk of infection by about an additional 50 percent, and a second dose stabilized the additional protection over the six months following vaccination.

Although vaccination increases protection, Nordström thinks the immunity offered by infection alone is worthy of consideration. "Perhaps we should have immunity passports instead of vaccination passports. So you are considered immune—and less likely to transmit the disease—if you have been fully vaccinated or if you have had a documented previous infection," he says.

Epidemiologist Victoria Hall of the U.K. Health Security Agency in London and her colleagues performed the third study by tracking infections in thousands of healthcare workers from March 2020 to September 2021. The researchers found that previous infections prevented more than 80 percent of the COVID cases that otherwise would have been expected in the year after infection, but protection waned to around 70 percent after a year. Study participants who received two doses of the Pfizer-BioNTech or Oxford-AstraZeneca vaccine after an infection had nearly 100 percent protection for at least six to eight months following the second dose. "Protection declined over time after vaccination, as well as after infection, but remained persistently high in those with hybrid immunity," Hall wrote in an e-mail to *Nature*.

Miguel Hernan, an epidemiologist at the Harvard T. H. Chan School of Public Health, says the studies show the near-universal benefit of full vaccination. Some nations have issued guidelines that encourage people who have had COVID to receive only a single vaccine dose: a move that "may be justified in a setting of vaccine scarcity but not otherwise," Hernan wrote in an e-mail to *Nature*.

VARIANT MIGHT CHANGE THE GAME

Dan Barouch, a virologist at the Beth Israel Deaconess Medical Center in Boston, says the findings are in line with previous research. "Vaccination following infection, or infection following vaccination, results in particularly robust antibody responses," he wrote in an e-mail to *Nature*. But Barouch notes that all three studies draw on data collected before the Omicron variant emerged. He and others caution that past infections will provide imperfect protection against emerging strains.

Dan Kelly, an infectious disease epidemiologist at the University of California, San Francisco, underscores that concern. Omicron is so different from the strains analyzed in the studies that the findings might not apply to people who were infected with Omicron after being vaccinated. His advice to people who fall into this category: "Just be really careful."

—Saima May Sidik

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Guinea Worm Disease Nears Eradication

Just 14 cases of the scourge that once infected millions of the world's poorest people were reported last year. But infections in animals complicates efforts to stamp it out

Man collecting water from Guinea worm–infested pond in Niger, West Africa.

Charles O. Cecil/Alamy Stock Photo

While the COVID-19 pandemic continues to rage around the world, another disease could be on its way out. Only 14 cases of infection with Guinea worm—a parasite that causes painful skin lesions—were reported in humans in 2021.

This is the lowest tally ever for an infection that, as recently as the 1980s, was found in more than 20 countries and infected 3.5 million people a year—however, a remaining reservoir for the parasite in animals means eradication could be a while off, if indeed it is possible, some scientists say.

"It's pretty amazing," says Adam Weiss, director of the Guinea Worm Eradication Program of the Carter Center, which is headquartered in Atlanta, Ga. The center announced the numbers in late January. "Fourteen people on a planet of almost eight billion. It's mind-bending to think about."

The reduction—nearly a 50 percent drop compared with the 27 cases reported in 2020—is the result of a nearly 40-year effort by international organizations and national governments to rid the world of Guinea worm, Weiss says. If it succeeds, the condition will join smallpox and rinderpest (a virus that mainly infected cattle and buffalo) as the only diseases to have been purposefully eradicated in human history.

This progress is "remarkable," says Julie Swann, a disease modeler at North Carolina State University—especially given that there is no recognized treatment or vaccine for the parasite. Instead eradication campaigns have focused on preventing transmission, she says.

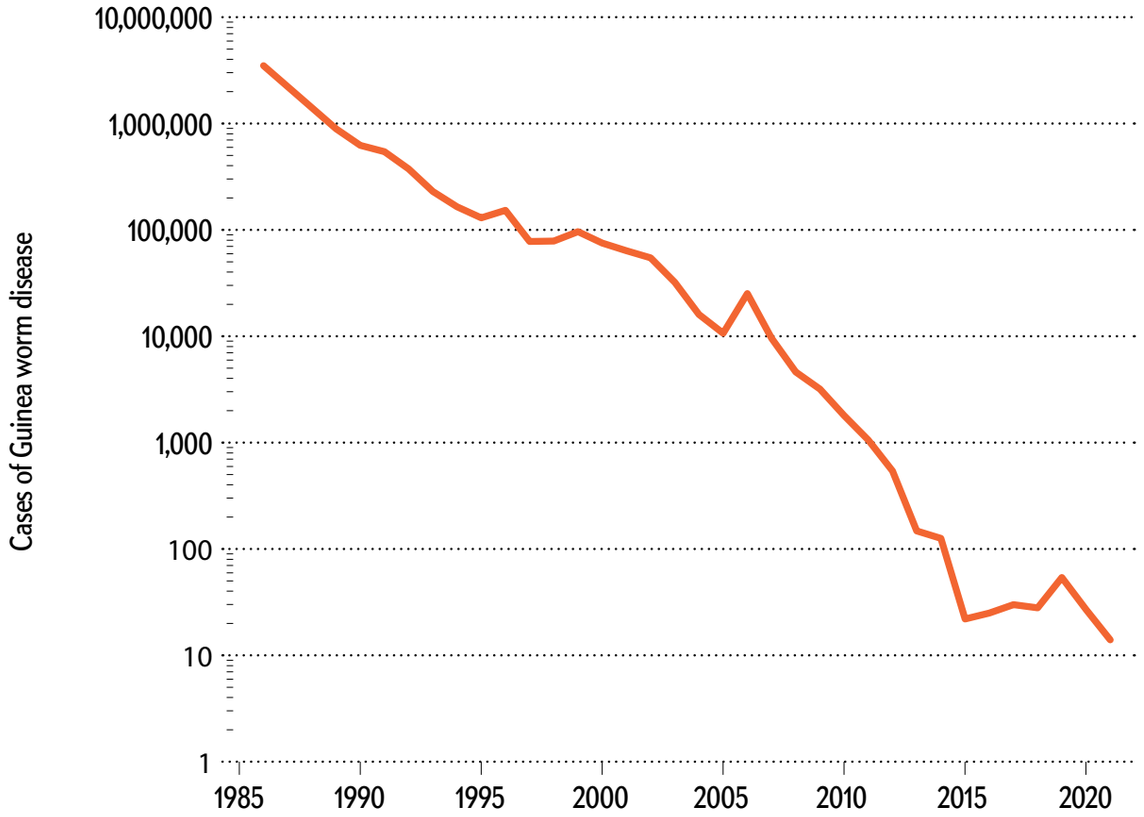
TRACK AND ELIMINATE

People and some animals, including cats, dogs and baboons, become infected with Guinea worm by drinking water that is contaminated with its larvae. After spending a year growing inside the host, the parasite—which can be up to one meter long—pushes through the skin of its host and waits to come into contact with water to release its larvae. The worm's escape is painful and can last for up to six weeks, sometimes preventing people from working or even walking.

But the recognizable nature of Guinea worm disease also makes the parasite easy to detect. In Chad, where seven of the 14 cases were re-

On the Way Out

Guinea worm disease is one of eight conditions that the International Task Force for Disease Eradication thinks could be eradicated in coming decades, considerably improving quality of life for millions of the world's poorest people.



ported last year, field agents create a network to track contaminated water sources, says Philippe Tchindebet Ouakou, coordinator of the nation's Guinea Worm Eradication Program, who is based in N'Djamena. They then prevent people from drinking the contaminated water and use pesticides to disinfect it.

Similar approaches have been used in countries such as South Sudan, Mali and Ethiopia, where the remaining seven detected cases in 2021 occurred. These methods are what have kept case numbers low, Ouakou says, and could be used to tackle other endemic diseases.

But Swann isn't entirely convinced that eradication is possible: she says that it's hard to control diseases that have animal reservoirs, pointing out that there were 790 reported cases of Guinea worm infection in dogs in Chad alone last year.

But animal cases were also down by 45 percent in 2021, and Weiss remains optimistic that eradication is within reach. He says that eradication programs are tackling animal reservoirs by tethering dogs to curb the spread of the parasite. Weiss adds that baboons are probably contracting Guinea worm from water contaminated by dogs, so controlling the parasite in dogs could help to rein in its spread in wildlife.

"I absolutely believe Guinea worm is eradicable," he says. "It will take more work, but if we couldn't do it, I'd be the first one to say it."

The International Task Force for Disease Eradication currently has eight diseases identified as potentially eradicable. In addition to Guinea worm, these are poliomyelitis, mumps, rubella, lymphatic filariasis, cysticercosis, measles and yaws.

—Freda Kreier

This article is reproduced with permission and was first published in Nature *on February 11, 2022.*

A Simple Solution Would Make COVID Antivirals More Accessible, Pharmacists Say

The Biden administration's Test to Treat program aims to make the treatments available at pharmacies, yet it requires a medical provider to prescribe the drugs

People in the U.S. who suspect they have COVID may now be able to get tested and treated much more quickly, thanks to a new federal program announced by President Joe Biden in his March 1 State of the Union address. The initiative, known as Test to Treat, allows people to take a COVID test at certain pharmacies and other sites—or send in the results of an at-home test—and receive a prescription for antiviral pills from medical providers at the same location.

In March participating pharmacies began distributing two antiviral medications: Pfizer's Paxlovid and Merck's molnupiravir, which are, respectively, 88 and 30 percent

"Just 14 Cases: Guinea Worm Disease Nears Eradication," by Freda Kreier, in *Nature*; February 15, 2022; Source: Carter Center

effective at preventing hospitalization and death from COVID when given within five days of symptom onset.

Both medications are most effective when administered soon after a person becomes infected with SARS-CoV-2, the virus that causes COVID, so the ability to start treatment without visiting a doctor's office could be game-changing for many patients. "Any efforts that go toward improving that efficiency are very welcome," says Julie Ann Justo, an infectious disease clinical pharmacist at the University of South Carolina.

But Justo and others worry that the Test to Treat program's impact will be limited because it does not allow pharmacists to prescribe the drugs. Although more than 41,000 pharmacies in the U.S. participated in a federal partnership program to administer COVID vaccines, far fewer have an attached clinic where a physician, nurse practitioner or physician's assistant can prescribe the antivirals, as required by the U.S. Department of Health and Human Services—and the department currently describes only hundreds of pharmacy sites taking part in Test to Treat.

Justo and others say that is a missed opportunity: In September 2021 HHS amended its policies to allow licensed pharmacists to prescribe COVID therapeutics. Many states already allow pharmacists to prescribe particular medications, including birth control and the opioid overdose drug naloxone. And several allow pharmacists to adjust the dosage of medications for conditions after consulting with a physician.

Under the Test to Treat program, people can get tested for COVID—and receive treatment—at select pharmacies and other locations.

A positive COVID test could eliminate the need for a physician's diagnosis. Nevertheless, the Food and Drug Administration's current emergency use authorizations for Paxlovid and molnupiravir permit only health-care providers to prescribe the drugs. The HHS did not respond to requests for comment.

Many pharmacists say that hurdle could be easily overcome. A March 8 letter to Biden signed by 14 professional pharmacy organizations advocated that Test to Treat should give pharmacists prescribing authority for COVID antivirals. "Pharmacists are clinically trained medication experts and are the primary health-care professionals responsible for ensuring safe medication use," it said. "Unfortunately, rural and underserved communities are less likely to benefit from your test to treat approach because of this limitation."

But medical organizations have opposed the idea. A March 4 statement from the American Medical Association, attributed to its president Gerald Harmon, said that "the pharmacy-based clinic component of the test-to-treat plan flaunts patient safety and risks significant negative health outcomes."

Harmon added that, despite the antivirals' effectiveness, Paxlovid can interact with numerous other drugs that a patient might be taking, and molnupiravir may affect bone growth in young people. "Leaving prescribing decisions this complex in the hands of people without knowledge of a patient's medical history is dangerous in practice and precedent," the AMA statement said.

The statement enraged pharmacists and patient advocates. Matthew Cortland, who works on health-care and disability issues at think tank Data for Progress, says the AMA's position "seems to me to be much more about physician ego"

George Frey/Getty Images

than serving disabled, chronically ill, immunocompromised or older Americans. "The notion that somehow pharmacists are ill-equipped to navigate [drug] interactions when that's literally what their doctorate is in is laughable and absurd."

Jacinda Abdul-Mutakabbir, an infectious disease pharmacist at Loma Linda University, who works on health-care equity issues, is among those disappointed by the Test to Treat program's limited scope. People of color, particularly Black, Hispanic and Native American individuals, are more likely to be hospitalized and die from COVID than white individuals but are less likely to receive novel therapeutics or to have a health-care provider. Allowing patients to receive prescriptions at a local pharmacist, she says, would be a good way to overcome the inequitable distribution of treatment. "This was something that may have allowed for some type of equity, some type of parity, and now we're once again in that exact same spot," she says.

Another problem is the drug supply. The U.S. has ordered a total of 20 million Paxlovid courses from Pfizer. In March the White House asserted that four million of them were available, with an additional one million coming in March and 2.5 million in April. But the federal spending bill passed on March 15 does not include money for further purchases. In a press briefing that day, a White House official said the administration will not be able to buy more pills without additional funding.

Even if pharmacists are given prescribing authority under Test to Treat, pharmacies will need to work out some kinks, such as providing places for patients to isolate while receiving their test and prescription to avoid spreading COVID and ensuring that pharmacists have access to patients' full medical records. "This is a country that put human beings on the moon," Cortland says. "You cannot convince me we are incapable of safely running a test-to-treat program nationwide."

Still, Justo is hopeful that the HHS will eventually move to allow pharmacists to prescribe the drugs. "It's not whether physicians or pharmacists should be the ones prescribing," she says. "I think we need all hands on deck. We need as many opportunities as possible for patients to receive health care."

—Sara Reardon

Even Mild COVID Can Increase the Risk of Heart Problems

Scientists are just starting to unravel the disease's long-term cardiac effects

Scientists have long been aware that respiratory infections—such as influenza or certain types of coronaviruses—can trigger heart disease. This happens because they cause inflammation, which plays a major role in cardiovascular problems.

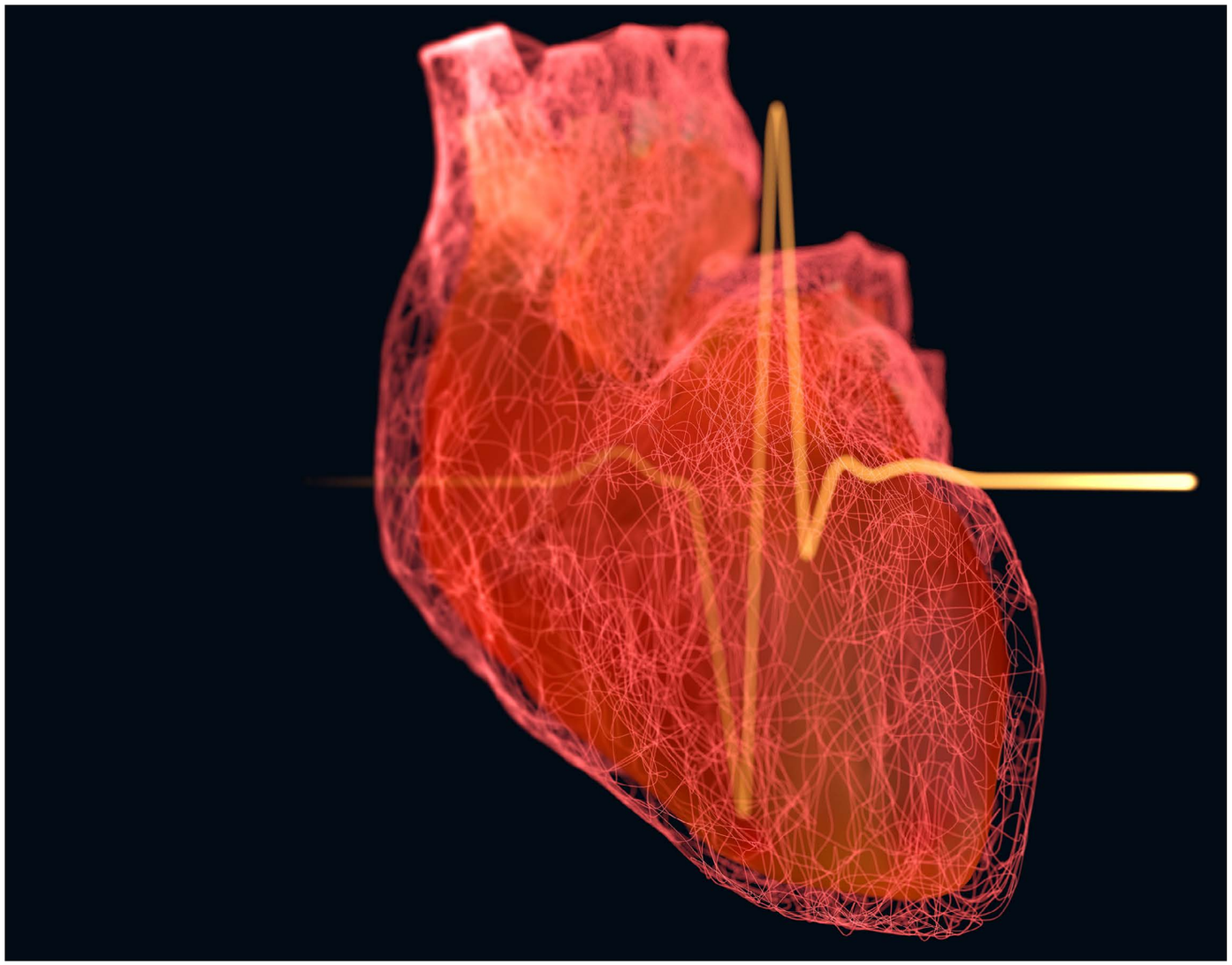
Even before the first case of COVID-19 had been confirmed in the U.S., interventional cardiologist Mohammad Madjid began looking into the potential effects of coronaviruses on the cardiovascular system. Madjid, an associate clinical professor of medicine at the University of California, Los Angeles, expected to see a similar increase in heart complications associated with COVID. "I knew that was going to happen because I'd seen this during influenza epidemics," he says. As far back as 2004, during the avian flu outbreaks in Asia, he urged public health organizations to consider cardiovascular issues in pandemic preparation plans.

Two years into the COVID pandemic, it is becoming clear that the cardiovascular impact of SARS-CoV-2, the coronavirus that causes COVID, is not restricted to people who have had severe COVID. Even those with mild disease appear to be at a higher risk of heart problems one year after infection, according to one of the largest studies to evaluate the long-term cardiovascular outcomes of COVID. The study was published in February in *Nature Medicine*.

The findings surprised the researchers. "I went into this assuming there was going to be some risk but primarily in people who had very severe disease and needed to be hospitalized in the acute phase of the infection," says co-author Ziyad Al-Aly, chief of research and development at the U.S. Department of Veterans Affairs (VA) St. Louis Health Care System and a clinical epidemiologist at Washington University in St. Louis.

A SERIOUS PUBLIC HEALTH PROBLEM

Al-Aly and his colleagues crunched the numbers on heart and other



Vertigo3d/Getty Images

cardiovascular issues during the first year after infection among 153,760 COVID patients from the national health-care databases of the VA. The researchers compared these patients with two control groups: a contemporary cohort who never became infected and a historical group from before the pandemic.

Overall, the risk of any heart complication over the course of one year was 63 percent higher in people who had gotten COVID compared with those in the contemporary control group. At the end of a year, there were 45 additional cardiovascular events—such as stroke or heart failure—per 1,000 people among those who tested positive for COVID. The comparison with historical data yielded similar results: the risk of cardiovascular problems in the group that had COVID was 58 percent higher than what was seen in the prepandemic control group.

When the researchers looked at people with mild COVID specifically, they found that this group had a 39 percent higher risk of developing heart problems, compared with the contemporary control group, or 28 additional cardiovascular problems per 1,000 people in 12 months.

That is a much lower burden than that seen in COVID patients who were hospitalized or admitted to intensive care. Still, the increased risk is not trivial. Compared with those who were not infected, patients with mild disease had more than three times the risk of myocarditis, an inflammation of the heart muscle, and twice the risk of pulmonary embolism, a blood clot that ends up in a lung artery and blocks blood flow.

"It is not only surprising but also profoundly consequential that the risk is evident even in those [who had mild infections]," Al-Aly says. Such cases make up the vast majority of COVID infections—within the study's population, 85 percent of those diagnosed with the disease were not hospitalized. "That's what makes this likely a serious public health problem," he says.

A much smaller retrospective study, described in a preprint paper that has not yet published or peer-reviewed, also found that COVID patients, including asymptomatic ones, had an increased risk of cardiovascular problems six months after infection. The estimated risk of heart complications after COVID matched that seen in Al-Aly's study, says cardiologist and biostatistician Larisa Tereshchenko, a researcher at the Cleveland Clinic Lerner Research Institute and lead author of the smaller study. "Despite

differences in population and definition of outcomes, [Al-Aly's team] came to a very similar estimate of absolute risk, which I found quite exciting because it supports the results of each study," Tereshchenko says.

Interestingly, when another group of researchers searched for cardiovascular abnormalities in patients with mild COVID, they did not find differences in the amount or type of abnormalities in those who had had COVID versus those who had not. Thomas Treibel, an associate professor of cardiology at University College London, and his colleagues at COVIDsortium, a group of immunologists, infectious disease doctors and scientists studying the pandemic in the U.K., recruited 149 otherwise healthy health-care workers. "We matched people who never had COVID with people who had COVID and put them all into an MRI [magnetic resonance imaging] scanner to look at cardiovascular damage," he says. "Across the board, we saw no difference in the cardiac function [or] any evidence of myocarditis or heart damage. And I think that was very reassuring," Treibel says.

How can scientists reconcile those findings? Tereshchenko believes that looking at patients' clinical outcomes is more important than cardiac imaging in this context. "When a patient is hospitalized with heart failure, acute infarction, acute arrhythmia, cardiac arrest … that is always more important than intermediate biomarkers" such as imaging, she says.

COVID'S LONG-TERM HEART BURDEN

While it is very likely that inflammation plays a role in the cardiovascular events seen in people with COVID, it is still a mystery why some individuals continue to be at increased risk long after SARS-CoV-2 has left their bodies.

One hypothesis is that the virus simply does not leave. "There are people who proposed the idea that the body might not fully clear the virus and will remain in its 'preference sites,' provoking low-grade inflammation," Al-Aly says. Another hypothesis, he notes, is that the immune response to the virus might go awry, damaging the heart.

An important question is whether SARS-CoV-2 directly infects the heart muscle, Madjid says. Scientists have shown it is possible to infect heart cells grown in a lab dish with the virus. This finding could explain some post-COVID cardiovascular problems. "The interesting distinction between influenza and COVID is that in COVID, we get less involvement of the heart arteries but more involvement of the heart muscle," he says.

"What we don't know—and I'm speaking as a cardiologist—is how many of those patients with long COVID actually have cardiac involvement."
—Bernard Gersh

SARS-CoV-2 also makes the blood clot more. "We see evidence of deep vein thrombosis and pulmonary embolism. And I think that's important because those people who have these micro clots or big clots might go on to have serious problems for a long, long time," Al-Aly says.

There is also a growing body of evidence suggesting that COVID affects the vascular endothelium, the inner lining of blood vessels, according to cardiologist Bernard Gersh, a professor of medicine at the Mayo Clinic College of Medicine and Science. "This leads to what is called microvascular dysfunction of the small vessels, which may not dilate or constrict the way they should," Gersh says. That could explain why long-lasting post-COVID symptoms are not restricted to the heart.

"Suffice it to say, there are many studies ongoing trying to understand the mechanisms of long COVID," Gersh says. But researchers have yet to pin down the most likely mechanisms causing post-COVID heart disease.

LONG COVID AND THE HEART

When it comes to "long COVID"—a constellation of symptoms, including fatigue, shortness of breath, brain fog and anxiety, that persist for several months—it is still difficult to establish an association with cardiovascular health.

"What we don't know—and I'm speaking as a cardiologist—is how many of those patients with long COVID actually have cardiac involvement," Gersh says. "Just because they have palpitations doesn't mean there's

structural damage to the heart."

It is definitely plausible that the typical presentation of long COVID, which can include fatigue and shortness of breath, may be intertwined with cardiovascular problems. For example, someone with heart failure may have reduced blood flow to the brain, which may cause brain fog. But at this point, it is difficult to disentangle that relationship, Al-Aly notes.

The problems seen in Al-Aly's and Tereshchenko's studies—including stroke, heart failure and acute coronary disease—are not happening only in people with recognizable long COVID. A person might have a mild case of COVID, appear to recover completely and still be at a higher risk for cardiovascular problems months down the road.

"Unfortunately, the risk estimate is high," says Tereshchenko, adding that these studies suggest the heart risks from COVID may be on par with those from smoking.

Al-Aly agrees. "People think of cholesterol, blood pressure and diabetes as risk factors for heart problems. We need to add COVID-19 to that list," he says.

—Mariana Lenharo

Discovery of New HIV Variant Sends Warning for COVID Pandemic

Infectious disease expert William A. Haseltine cautions that a coronavirus variant could emerge with the transmissibility of Omicron and the deadliness of the original SARS

As SARS-CoV-2, the coronavirus that causes COVID-19, has spread throughout the world, many observers have failed to take note of the millions of illnesses and deaths caused by HIV—another virus that has approached pandemic status during its history. Now an HIV variant that is more virulent and transmissible has been discovered in the Netherlands, where it apparently has been circulating for decades, according to new research. Luckily, none of the variant's new mutations make it resistant to widely used therapies. But the finding may offer a warning for how the COVID pandemic could proceed in the coming months: viruses do not necessarily evolve to become milder.

Without treatment, people infected with the newly identified HIV variant have more than three to more than five times higher levels of the virus in their blood, making them more infectious. Plus, their immune system deteriorates twice as fast, setting them on a course to potentially develop AIDS years earlier than people with other versions of HIV. These findings, published in *Science,* indicate the newfound variant carries more than 500 mutations scattered across its genome—although it is unclear how they enable the virus to cause more severe disease.

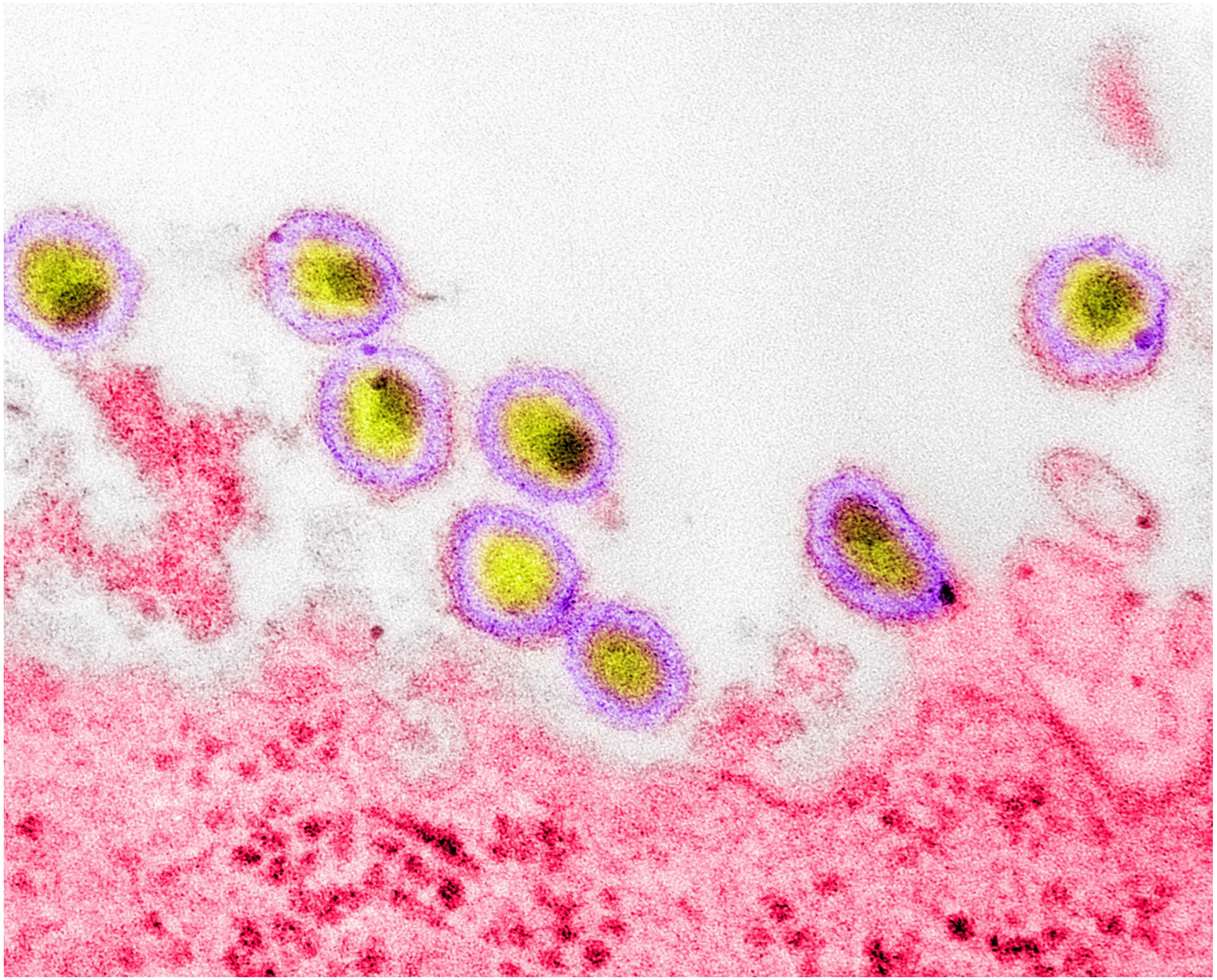
William A. Haseltine, an infectious disease researcher who founded Harvard University's cancer and HIV/AIDS research departments and now chairs think tank ACCESS Health International, has written extensively about the potential of SARS-CoV-2 assuming a more dangerous form. Haseltine spoke with *Scientific American* about why a more virulent variant of HIV—a virus that has been known for nearly half a century—is just coming into focus now, whereas the new coronavirus has spawned several "variants of concern" in a matter of months. [*An edited transcript of the interview follows.*]

What does the discovery of a more virulent HIV variant tell us about how viruses, including SARS-CoV-2, evolve?

We've known that all viruses adapt. The way they adapt is much like how we use artificial intelligence to solve complex problems: the machine throws a lot of random combinations at something, and the one that works best is the one that survives.

With HIV, [its evolution has] been a long, drawn-out process because the virus is poorly transmissible. It takes, on average, 100 sexual contacts for a man to give it to a woman and 200 contacts for a woman to give it to a man. The process is a slower-evolving one—not because the virus doesn't change but because the replication cycles can be quite long. For Omicron, those cycles can take hours or days at the most. The virus can be transmitted by a person simply breathing the air somebody else breathed half an hour ago.

In the past year or so SARS-CoV-2 has produced several different variants of concern. How worried should we be that more virulent versions of the virus are yet to emerge?



HIV-1 (*shown here*) was identified nearly 40 years ago. In February 2022 researchers reported the discovery of a more virulent variant of the virus.

Callista Images/Cultura Creative Ltd/Alamy Stock Photo

First of all, the virulence of SARS-CoV-2 has been very stable—with the exception of Delta, which is twice as likely to land you in the hospital. Delta was a warning shot across our bow, showing the virus can become both more transmissible and more virulent. There is nothing that we know of that restrains this virus from becoming as lethal as its cousin SARS-CoV-1. We still have no clue whether one genetic change or many make SARS-CoV-1 so much more virulent than SARS-CoV-2. As long as we are in the dark about what it is that determines the virulence of the virus, we have no idea which direction the next variant will come from. So I've been telling policy makers to be optimistic about the upside but prepare for the downside.

Are some viruses poised to produce more variants of concern than others?

Yes, RNA viruses [such as HIV and SARS-CoV-2], in general, make more mistakes [and thus enable more opportunities for evolution] than DNA viruses. Your cells have elaborate machinery to fix mistakes in DNA, which must last a long time

to be inherited, whereas RNA is effervescent and plays a more transient role in cellular life. It turns out that SARS-CoV-2 has a proofreading enzyme that can correct mistakes, so people thought that would protect against variation. They were incorrect. One of the major errors people made in underestimating this virus was the extent to which it can change.

HIV and SARS-CoV-2 are both RNA viruses. Do the factors driving their evolution differ and, if so, how?

The selective pressure on a virus is to survive, just like it is for any other organism. What the virus wants to do is get from one person to another—get in and get out. Because HIV is so poorly transmitted, its best strategy is to get in and stay there for a very long time and rely on a predictable behavior—sex—to get out.

For SARS-CoV-2, the virus depends for its existence on reinfecting people who have been infected the year before. We are fighting millions of years of evolution of an organism that knows how to fool our immune system and get into us again and again. One thing we have seen the viral variants doing is getting faster and faster [at transmission]. Delta is faster than Alpha. Omicron is faster than Delta. And BA.2 Omicron is faster than BA.1 Omicron. There are many ways for this virus to mutate to increase its transmissibility. Whether any of those will affect virulence is unclear.

—Marla Broadfoot

How to Make Smart Decisions about COVID Risk-Benefit

Scientific American asks experts in medicine, risk assessment and other fields how to balance the risks of COVID with the benefits of visiting public indoor spaces

By Devabhaktuni Srikrishna

Jeff J Mitchell/Getty Images

Devabhaktuni Srikrishna is founder of Patient Knowhow, a Web site that aims to uncover reliable and easy-to-use information about disease prevention, transmission, causes and treatment. Follow him on Twitter @sri_srikrishna

As COVID cases declined across the U.S. in recent months and mask mandates were lifted, more people returned to restaurants, concert halls and offices maskless. But the novel coronavirus's Omicron subvariant BA.2—which caused another wave in Europe and China—and related variants threaten to reverse that progress here. In April dozens of attendees (including high-ranking government officials) tested positive for COVID after attending a dinner in Washington, D.C. The safest option, of course, is to continue avoiding crowded indoor activities. But there remains a lot of interest in safely enjoying bars, cafes and other higher-risk venues that offer the benefits of social interaction.

Scientific American asked experts in epidemiology, medicine, risk assessment and aerosol transmission for advice on how to decide which risks we are willing to take. These decisions are based on assessments of personal risk, community risk and exposure risk—and the steps one can take to take to mitigate them. Personal risk refers to the danger of contracting COVID faced by an individual and the members of their household. Community risk is the current likelihood of encountering COVID among members of one's community. And exposure risk accounts for the increased chances of catching COVID at a particular venue based on airflow characteristics of the space itself and other people's behavior.

Here is what experts say about managing these risks while maintaining some of the benefits of public life.

How should people factor personal risk for severe COVID into their decisions?

The number-one predictor of having a severe case of the disease is age, followed by the presence of comorbidities and immunocompromised status, according to Katelyn Jetelina, an epidemiologist who studies COVID risks at the University of Texas Health Science Center at Houston. Using data from the U.S. Centers for Disease Control and Prevention, she estimates that even vaccine-boosted people ages 50 to 64 are more than 10 times more likely to die from a severe breakthrough case than 18- to 49-year-olds with the same vaccination status. Donald Milton, a physician and clinical researcher who studies respiratory viruses at the University of Maryland, highlights recent research showing that in households with a person who was infected with the Omicron variant (B.1.1.529) of the COVID-causing virus SARS-CoV-2, 43 to 64 percent of people became infected as well, depending on whether the initially infected person was boosted, fully vaccinated or unvaccinated. Jetelina cautions that we also need to account for the personal risks of the people with whom we live in our own risk assessments.

In general, people should discuss personal COVID risk with their doctor; it depends, in part, on which medications they take. Ethan Craig, a rheumatologist at the University of Pennsylvania, cares for patients who are immunosuppressed because of disease or medication and studies COVID risks in that population. One such immunosuppressive drug, rituximab, "knocks out your ability to make antibodies against new viral exposures and impairs your ability to make a response to a vaccine," he says. Craig adds that such patients usually take precautions of their own accord, such as wearing high-filtration N95 masks, and "if anything, I end up having to talk people down sometimes and be like, 'Look, it's okay to go to the grocery store.'" For some people, however, even this amount of exposure could be considered an unacceptable risk.

How does the risk of dying from COVID compare with the risk of dying from other causes linked to common activities?

Jetelina estimates that, for people between the ages of 18 and 49 who are boosted, the risk of dying from COVID is roughly equal to the risk of dying when someone drives about 10,000 miles. COVID risk goes up substantially with age and with being unboosted or unvaccinated. Thanks to vaccines, infection-induced immunity, therapeutics, better care and other factors, the relative risk of dying from COVID if you catch it is now, broadly speaking, comparable to that of seasonal flu, Jetelina says—but importantly, because you are more likely to catch COVID than flu, the absolute risk remains much greater. Jetelina recommends COViD-Taser's Relative Risk Tool, a resource funded by the National Science Foundation, that she helped to develop. It compares one's risk of death from the disease to such risk posed by other activities, including driving. Although it is a research tool, Jetelina says she can "really trust the science and mathematics behind it."

But Baruch Fischhoff, a professor of engineering and

public policy at Carnegie Mellon University and an authority on how to communicate health risks, cautions against using risk-risk comparisons to make choices without fully considering benefits or unquantified risks. Employers may also misuse such comparisons to compel employees to accept certain risks on the job, which is not exactly a choice. Currently risk calculators provide estimates based on retrospective data and may be unable to reliably weigh long-term complications of COVID.

How should one assess community risk?

There is no perfect way to measure community risk because it would take repeated random testing, so experts use other estimates: daily cases per 100,000 residents, test positivity rates and growth rates. Jetelina recommends using the *New York Times*'s tracker to look up community transmission for your county. She considers community risk high when there are more than 50 weekly cases per 100,000 residents. When the risk is lower than that, Jetelina—a healthy, young boosted person—feels comfortable taking off her mask indoors. "I will say it's taken a lot of time for me to be comfortable with that," she says. "Once transmission rates of those indicators start increasing a bit, I'm putting my mask back on." Others suggest a slightly higher risk threshold of 10 daily (or 70 weekly) cases per 100,000 residents.

Daily city or county case counts are often an undercount because not everyone is getting tested and home test results are not always reported. As a work-around, health authorities use the "test positivity rate," or "percent positive"—the percentage of COVID tests reported to public health authorities that were positive. If that number exceeds 5 percent, it is widely considered high risk for community transmission (provided the amount of testing in that area is adequate). But the community sample used to measure test positivity likely includes many people who seek out testing because they are currently experiencing COVID symptoms. So test positivity is typically higher than the infection rates among the people you might encounter in a cafe or grocery store, most of whom do not have any symptoms but could still be infectious.

"Once transmission rates of those indicators start increasing a bit, I'm putting my mask back on."
—Katelyn Jetelina

Still, Robert M. Wachter, a professor and chair of the department of medicine at the University of California, San Francisco, says there is no test positivity threshold that separates "safe" from "not safe" because it also depends on other factors, such as whether the benefit outweighs the risk to you personally, the number of people you will be exposed to, and the closeness and duration of exposure.

Because of these large uncertainties in test coverage, Gerardo Chowell, a professor of mathematical epidemiology at Georgia State University, prefers to look at the general trend in daily COVID cases, hospitalizations and deaths, or percent positive. "When the trend is going up, you're seeing the transmission chains expand," Chowell says. "That means that the reproduction number"—the expected number of secondary infections from each infected person—"must be greater than one. If it is increasing, that's probably the time when [one has the] highest risk of acquiring COVID in a social setting without a mask," he says." Wachter points out that, where available, wastewater surveillance may also give an early indication of COVID trends.

What is known about exposure risk in different settings, such as bars or movie theaters?

Linsey Marr, a professor of civil and environmental engineering at Virginia Tech and one of the world's leading experts on airborne transmission of viruses, says COVID risk in indoor spaces exists on a continuum. It is believed that reducing the amount of virus inhaled (that is, the inhalation dose) makes infections less likely or illness less likely to be severe. Marr says one of the riskiest settings is an aerobic exercise studio: if somebody is infected, they are going to be exhaling more virus, and everyone else will be inhaling at a faster rate, too. Breathing heavily produces up to 10 times more aerosol particles that carry viruses than breathing normally, according to Richard Corsi, an expert on indoor air quality and dean of the College of Engineering at the University of California, Davis.

Marr says that talking in bars expels a similar number of respiratory particles as coughing, "so it's like everyone's in there coughing together." Craig uses smoking as an analogy for aerosols exhaled during breathing and talking. In other words, "if a person was smoking in this place, would I be able to smell it?" he says. In movie theaters, there is risk of exposure from those seated immediately around you, but because of limited talking and, typically, a high ceiling, there is a lot more dilution of the air. So such a theater may be less risky than other crowded indoor venues. By that reasoning, museums, big-box retailers and grocery stores with high ceilings tend to be relatively safer as well.

Places with rapid rates of ventilation and filtration—such as some subways—are also much lower risk. The Bay Area Rapid Transport (BART) system in the San Francisco Bay Area, for example, filters the air more than 50 times an hour with "virus-trapping MERV-14 air filters" inside each car. An Italian study of schools found that

classrooms with ventilation systems that exchanged air six times per hour reduced infections by more than 80 percent, but many classrooms in the U.S. fail to meet this standard. Corsi characterized current public health recommendations of four to six air exchanges per hour as "a little bit anemic … we can do better." He recommends owners or managers of crowded indoor spaces, such as classrooms, offices and bars, aim to filter or ventilate with fresh air at rates approaching 12 air exchanges per hour to reduce risks down to the level of an airborne isolation room in a hospital. Not all venues have the resources to do this, but the benefits increase with greater filtration rates, so the closer to this ideal, the better. In places with inadequate ventilation, consider bringing a portable high-efficiency particulate air (HEPA) purifier—or building your own using box fans and high-quality HVAC (heating, ventilating and air-conditioning) filters—to run nearby.

Although the virus is thought to be transmitted primarily through the air, there have been a few documented cases of surface transmission, so it remains a good idea to wash your hands frequently, Marr says.

How can one further reduce the risk of getting COVID from everyday activities?

Getting vaccinated and boosted protects against death, hospitalization and, to a lesser extent, catching and spreading the virus. To avoid infection, Wachter recommends wearing an N95 mask. He has observed that the risk of U.C.S.F. health-care workers—himself included—getting infected from their patients while wearing a well-fitting N95 is extraordinarily low. These respirators get close to filtering all of the virus, but they do not filter 100 percent. And if an N95 does not form an airtight seal with your face, it may allow unfiltered air into your lungs. So it is essential to try out and select N95 models that fit and seal to your face without gaps.

According to Wachter, one of the most important factors in overall COVID risk is whether "the person next to me has it."

What is the risk of taking your mask off in a restaurant or bar to take a sip or bite?

In the 1990s medical researcher Stanley Wiener, then at the University of Illinois College of Medicine, proposed that a person could use respirators to survive aerosolized biological attacks, taking it off briefly to consume food and drink. During the pandemic, many places have allowed masks (or N95 respirators) to be removed while actively eating and drinking. Removing an N95 momentarily for a bite or sip carries "some risk, but I think it's pretty tiny if you're exposed for three seconds," Corsi says, unless an infected person is "right in your face… and shedding a lot [of virus]." Provided community risk is low or trending downward, Chowell, too, feels comfortable briefly removing his respirator to eat or drink at a party.

What do we know so far about the risk of "long COVID"?

Ranu Dhillon, a physician at Brigham and Women's Hospital in Boston, who advises governments on infectious disease outbreaks, says he is seeing some patients with "a constellation of different types of symptoms after acute COVID infection," including young, boosted and relatively healthy people. Wachter cautions that some fraction of vaccinated individuals who get infected—which one study estimates to be around 5 percent and possibly higher—may continue to feel short of breath or fatigued or think less clearly than before. COVID may increase the risks of heart attack, stroke, brain abnormalities or the onset of diabetes. While there have been preliminary studies of the rates of long COVID, including risks of developing cardiovascular complications, Wachter says many of these involved unvaccinated people or infections with variants prior to Omicron. Provisionally, he likens these risks to 20 years of untreated high blood pressure or smoking and points out that one cannot know the risk of long COVID among vaccinated and boosted individuals until long-term studies have concluded, which will take years.

How can we balance these risks with the benefits of socializing and being with others?

According to Wachter, one of the most important factors in overall COVID risk is whether "the person next to me has it." He acknowledges that if someone is both vaccinated and boosted, it is not irrational for that person to decide that the mental energy and angst of calculating risks and taking precautions is high enough—and the risks of getting sick or dying from COVID are low enough—that they will go back to "living like it's 2019"—as people in many parts of the country already have. He still worries about the risk of long COVID, though. Milton says that many people "don't want to wear masks forever" and that we should work to make our built environments better at stopping aerosol transmission. He says people also have to decide whether to wear a high-quality mask when they are around those at higher risk, such as the elderly or immunocompromised, or around other people in general, such as at a party. When community transmission is low, Chowell says he may feel comfortable removing his N95 at parties in some situations, such as to have a drink. "Then you find a way to still interact with people, and they smile back once in a while," he adds. ■

Mars Mission Could Bring Health Benefits on Earth

Flying to space takes its toll on the human body, and this has spurred new research on radiation and microgravity, as well as advances in remote medicine and telehealth, all of which have potential benefits for people on Earth

By Marion Renault

Canadian Space Agency astronaut David Saint-Jacques tries the Bio-Monitor, an innovative smart shirt designed to measure and record astronauts' vital signs.

Canadian Space Agency/NASA

Marion Renault is a freelance writer based in Brooklyn, N.Y.

A TRIP TO MARS WILL COST THE HUMAN BODY MORE THAN TIME. After the initial days of motion sickness, an out-of-this-world physiological transformation sets in. Without gravity's downward pull, muscles atrophy. The heart shrinks. The skeleton weakens. The immune system falters. Blood and other bodily fluids slosh headward, pressing on the eyes and impairing vision. Ninety-minute days disrupt an astronaut's circadian rhythm, as radiation scrambles the person's DNA.

"That's the price you pay," Canadian Space Agency astronaut David Saint-Jacques tells *Nature Medicine*. "It's tough on your body." As a medical professional and a spacefarer, Saint-Jacques has to balance two competing priorities every time he leaves the stratosphere. "Going to space is fun," he says. "But it's very, very bad for you."

Six months onboard the International Space Station (ISS)—the average mission length—takes an impressive toll. In that time frame, an astronaut's bones lose density, and arteries thicken and stiffen the equivalent of a normal decade of terrestrial aging. Over a six-month period an astronaut's internal temperature can rise by one degree Celsius as the person is exposed to the 375 chest x-rays' worth of radiation and becomes more susceptible to kidney stones, allergies and infectious diseases.

Even an astronaut's height changes in space, Emmanuel Urquieta, chief medical officer at the Translational Research Institute for Space Health at the Baylor College of Medicine, tells *Nature Medicine*. "We have been designed to live inside our bubble on Earth." Once we leave that safe haven, "pretty much every organ system gets impacted and affected," he says, "one way or another."

As space agencies prepare for a return to the moon in the coming decade—and after that, travel to Mars—space medicine research continues to be ambitious and boundary-pushing. "For an extreme environment, you need extreme approaches," Urquieta says. "You need solutions that sound crazy."

Earth dwellers should benefit from these innovations. "Yes, we'd like to go to Mars," Farhan M. Asrar, a professor of medicine at the University of Toronto and Trillium Health Partners and a faculty member at International Space University in France, tells *Nature Medicine*. When it comes to the technical accomplishment that will get us there, he asks, "How can we use those to benefit Earth and health care on Earth?" Already technologies developed to help astronauts survive—including telehealth, portable ultrasounds, air purifiers and gravity-compensating bodysuits, to name a few examples—have made their way down to terrestrial health-care settings.

"Space exploration can be the perfect excuse to scratch our heads," Saint-Jacques says, "and push medicine."

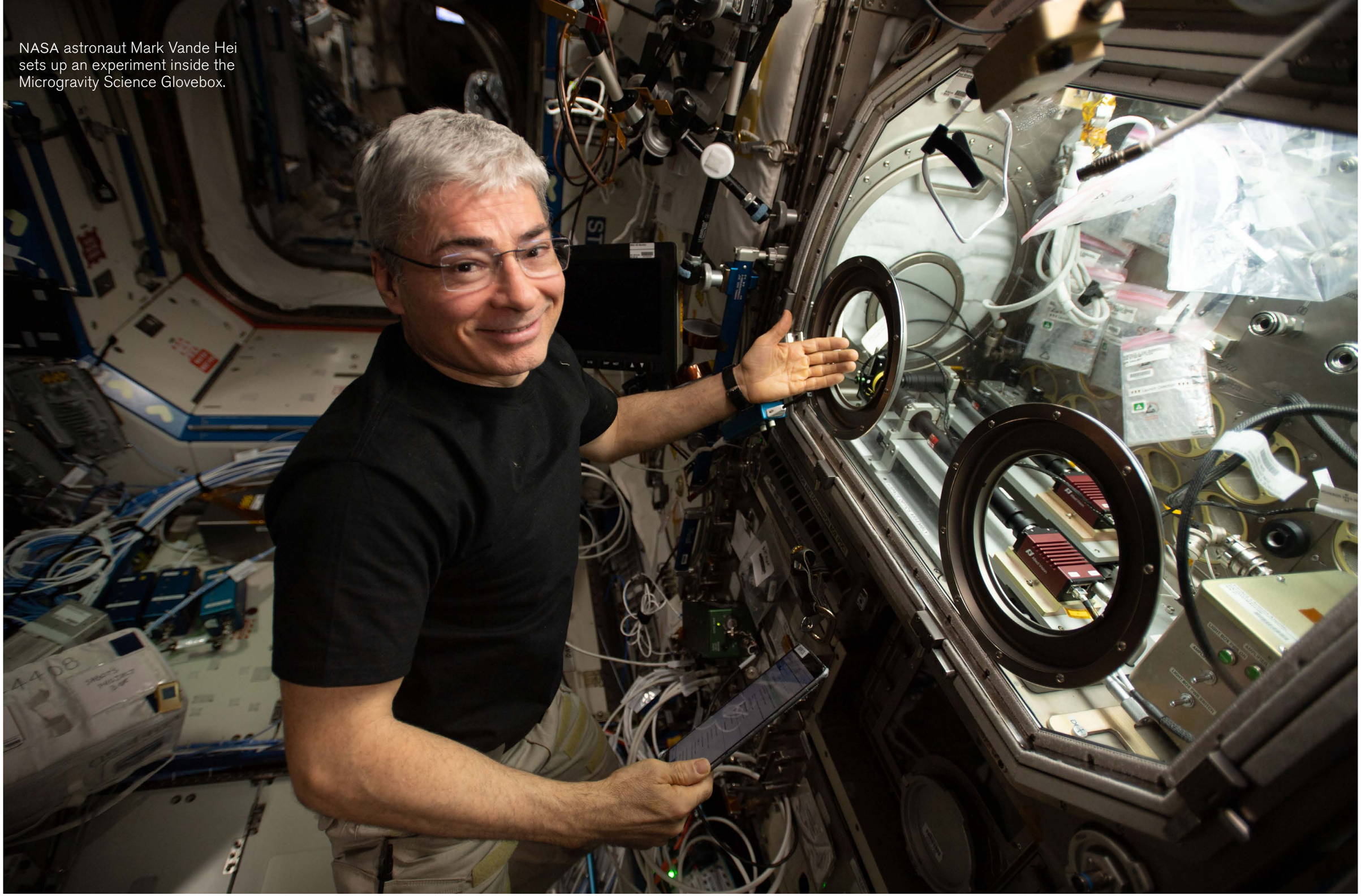
A TEMPLATE FOR TELEHEALTH

Making humans a spacefaring species has become a central challenge for space medicine, Thu Jennifer Ngo-Anh, research and payloads program coordinator for the European Space Agency, tells *Nature Medicine*. "It's not enough to just bring them there and get them back in one piece," Ngo-Anh says. Instead researchers are investigating ways to equip astronauts so they can serve as their own medical providers: monitoring their own health, diagnosing any issues, and treating them with whatever is onboard.

The ISS is 240 miles above Earth and has to serve as an all-in-one home, office, research laboratory, grocery store, pharmacy, gym and hospital. Regular supply flights from Earth bring food, experiments and medicines.

The farther humans venture from Earth, the more challenging supply flights will be. In recent years some researchers have focused on how to augment a spacecraft's stores with a biological foundry for pharmaceuticals: plants. By using genetically modified plants as chemical factories, astronauts could someday grow the medicine they need in space.

Communications pose another problem for deep-space voyagers. On Mars, communication delays with Earth could be as much as 20 minutes—one way. That means astronauts will not be able to depend on guidance from medical professionals at mission control or on resupplies of food or medicine across the multimillion-mile expanse. "They will need to diagnose and treat themselves without any reliance on Earth," Urquieta says.



NASA astronaut Mark Vande Hei sets up an experiment inside the Microgravity Science Glovebox.

NASA

Technology developed to help astronauts conduct basic medicine with limited tools and knowledge has already helped in the delivery of health care to remote places such as Antarctica, ships at sea or home care settings, which are hard to access and face a shortage of health-care workers and supplies. “We’re all hungry for medicine to come to us,” Saint-Jacques says. Take, for example, frail and homebound elderly people. “They might as well be in space, they’re so hard to reach,” he says.

In September 2021 the all-civilian, four-person crew of SpaceX’s Inspiration4 mission tested out the Butterfly iQ, a handheld ultrasound, taking images of their hearts,

lungs and urinary systems without any ground support. That same pocket-sized device has already been deployed in rural communities around the world where x-ray, CT and MRI machines are hours away. Other remote monitoring innovations such as miniature and body-worn scanning devices collect and track biomedical data from astronauts, such as breathing, heart rate, body temperature and blood oxygen levels.

This allows astronauts to identify health problems as soon as they arise. These same devices could autonomously monitor critically ill patients in the hospital around the clock. A portable, self-operable vision-testing tool developed for space could help astronauts deal with space-related changes in vision, as well as the billion-plus people worldwide who suffer from poor vision resulting from undetected and uncorrected eye problems.

Other breakthroughs have led to orbital lab testing systems that do not require an expert to operate. "They're paving the way so you don't have to go to a centralized laboratory or pull a whole vial of blood and wait a whole week for results," Urquieta says. These tests could have a positive impact in rural or isolated communities.

THE PERFECT GUINEA PIGS

On April 12, 1961, Russian cosmonaut Yuri Gagarin's 108-minute orbit of the planet marked the first episode in humanity's short history in outer space. At the time, scientists had a sense that its physical environment—the weightlessness, radiation, extreme temperatures and vacuum conditions—would be hostile to the human body. But the exact physiological impact of space travel remained an open question.

"Before the Apollo missions flew, the engineering community developed 0.999 reliability figures for all of the parts of the spacecraft and launch vehicles. They wanted me to do the same for [humans]," NASA flight surgeon Charles Berry later recalled. "I had repeatedly said that I could not do that for astronauts."

"Everything we do in space has a spin-off for Earth. If not 100 percent, close to 100 percent."
—Emmanuel Urquieta

Fewer than 600 people have followed Gagarin into space, but the understanding of how to safeguard the human body from its perils has transformed dramatically. That is thanks in part to astronauts who have conducted research (an estimated 3,000-plus science experiments) onboard the ISS or have participated in human experiments as test subjects.

Mark Shelhamer, a human spaceflight researcher at the Johns Hopkins University School of Medicine and former chief scientist of the NASA Human Research Program, says it is much easier to control an experiment on astronauts. Variables such as exercise and social dynamics are "all almost impossible to measure in a cohesive manner on Earth," Shelhamer says, but are easy to track in a spacecraft's strict confines. "We know what they eat, how much they sleep, their workload."

And whereas on Earth, researchers are resigned to hoping participants will be honest and follow a study's rules, astronauts are duty-bound to carefully and precisely carry out directions, often for their own safety. "They are very, very good at following procedures. They follow it to the letter," Urquieta says. "In a terrestrial trial, you don't have that luxury." Saint-Jacques agrees. "We're the perfect guinea pigs."

Health research conducted in space has thus far been severely limited by small sample sizes, the impossibility of blinding, and its participants' overwhelmingly white and male demographic. But some of those statistical and representation weaknesses could begin to improve as space travel becomes accessible to space tourists.

The Inspiration4 mission, for example, was led by the first Black woman to pilot a spacecraft, and it included a 29-year-old female survivor of cancer. During their three-day mission, crew members measured their heart activity, movement, sleep, blood oxygen saturation and cognitive performance. They also took ultrasounds of their organs, collected and analyzed their blood, and tested their balance and perception.

Shelhamer will study the Inspiration4 data to understand how the vestibular system, which helps the body maintain balance, operates in a weightless environment and after return to Earth. The research could eventually help people on Earth with conditions such as vertigo and is one example, Shelhamer says, of how "space is an acute form of all the things we face on Earth."

TO MARS AND BACK

A trip to Mars will require further medical advances so that astronauts can survive the journey there—and back again.

Researchers are exploring how to put astronauts in hibernation to reduce their metabolic rate, oxygen consumption, carbon dioxide production and caloric needs during the estimated three-year round trip to Mars. There is hope that this will inform terrestrial efforts to cryopreserve tissues and organs for transplantation. Instead of the current race to match donors with recipients in a limited window of time, cryopreservation could allow organs to be deposited in a frozen bank, to be withdrawn whenever needed.

A trip to Mars will also expose astronauts to years of cosmic-ray exposure, increasing their risk of cancer and damaging their cardiovascular and central nervous systems. "This kind of radiation is constant," Urquieta says. "Low dose but chronic." On Earth, exposure to radiation can be mitigated with lead aprons and thick slabs of con-

crete—solutions too heavy for space flight. Instead researchers are exploring molecular methods of boosting cellular repair in astronauts, such as gene therapy with an adeno-associated virus vector, which could protect astronauts against radiation before they leave the ground. Viral gene therapy to protect astronauts against radiation could prevent the need for onboard pharmaceuticals and could have long-lasting protection of several years' duration.

If successful, such viral gene therapy could have many applications on Earth, including helping to minimize the harmful effects of radiotherapy for patients with cancer by genetically shielding noncancerous cells from damage, leaving only the cancer exposed.

"Everything we do in space has a spin-off for Earth," Urquieta says. "If not 100 percent, close to 100 percent."

MERITS OF MICROGRAVITY

One of the greatest challenges of living in space is the microgravity environment, but this provides benefits for research. "There are advantages to taking gravity out of the equation," says Bryan Dansberry, program scientist for NASA's International Space Station Program Office, because it allows "stuff you can't easily do when you have 1g pushing down on you."

In microgravity, liquids do not need solid containers; they form floating spheres bound by surface tension. Fluid dynamics in microgravity are helping medical researchers study amyloid fibrils, the protein tangles that stubbornly accumulate in the brains of people with neurodegenerative diseases such as Alzheimer's and Parkinson's. On Earth, scientists struggle to grow amyloid fibrils in vitro because of their physical, chemical and electrostatic properties. This is where microgravity can come in handy. Early research shows it may be possible to grow and study amyloid fibrils in self-contained liquid drops in the ISS's microgravity environment. If amyloid can be grown, it can be understood, which could unlock understanding of the associated neurodegenerative diseases.

Microgravity slows the formation of crystals, so it is possible—and easier—to produce high-quality crystals in gravity's absence. These high-quality crystals can be used for structural biology studies. In addition, pharmaceutical investigations are exploring how to transform intravenous liquid treatments into a uniform crystalline form in space, which could pave the way to more drugs that are cheap, pure, injectable, fast-acting and shelf-stable—useful for astronauts but with plenty of applications on Earth.

Cell biology experiments are altered in microgravity, with stem cells retaining their stemness for a longer duration. This could improve individualized stem cell therapies that depend on large quantities of stem cells, which are difficult to grow in two-dimensional cell cultures. Researchers have already begun to test the feasibility of growing stem cells in space to harvest and use in clinics on Earth. Scientists will use the effects of microgravity to study how cancers grow, with experiments planned for China's new Tiangong space station. The hope is that this increased understanding of cancer cell biology, learned in microgravity, will lead to new treatments for cancer.

One field that is fairly advanced is the use of microgravity for engineering and materials science. Engineers are developing a system for manufacturing retinal implants, or artificial retinas, in space, where microgravity allows more uniform layering. Earth-bound efforts to bioprint transplantable materials have been stymied by gravity, Dansberry says, which can collapse lacelike networks of veins and nerves. In the future, space might provide the exact right conditions for printing out those delicate tissues.

"It's still sci-fi at this point," Dansberry says, "but we're taking first steps." SA

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A lab technician works on the production of molnupiravir, an oral antiviral drug that some countries have authorized for use against COVID-19.

Ziad Ahmed/NurPhoto via Getty Images

A Deluge of New Drugs for COVID

Two years into the pandemic, the pipeline for COVID-19 drugs is primed to pump out novel treatments—and fresh uses for familiar therapies *By Heidi Ledford*

Heidi Ledford works for *Nature* magazine.

IT TAKES LAWRENCE TABAK ABOUT 15 MINUTES TO RATTLE OFF ALL the potential COVID-19 treatments being tested in the clinical trial program he oversees: a lengthy, tongue-twisting list that includes drugs to disarm the virus, to soothe inflammation and to stop blood clots. Over the past two years the ACTIV program, run by the U.S. National Institutes of Health, has included more than 30 studies—13 of them ongoing—of therapeutic agents chosen from a list of 800 candidates. Several of the studies are due to report results in the first half of the year.

And that's just in his program; hundreds more are in progress around the world. Whether those results are positive or negative, Tabak says, 2022 is poised to provide some much needed clarity on how best to treat COVID-19. "The next three to four months are, we hope, going to be very exciting," says Tabak, acting director of the NIH. "Even when a trial does not show efficacy, that's still incredibly important information. It tells you what not to use."

Nearly two years into the pandemic, that information is still badly needed: with more than one million new infections and thousands of deaths around the world each day, COVID continues to strain health-care systems and exact a terrible human toll. Researchers have developed a handful of options—including two oral antiviral drugs, Paxlovid and molnupiravir, authorized in some countries in the past couple of months—that help in certain situations. But gaps remain, and researchers think that this year will bring new drugs and new uses for older drugs, including better treatments for mild COVID.

And although vaccines remain the most important way to rein in the pandemic, there is still a desperate need for better therapies to treat people who cannot—or choose not to—access the vaccines, whose immune systems cannot respond fully to vaccination, or who experience breakthrough infections. "The main tool in combating the pandemic is prevention, and the main tool in prevention is vaccination," says Taher Entezari-Maleki, who studies clinical pharmacy at Tabriz University of Medical Sciences in Iran. "But new medications can fill in when vaccines do not work—for example, against new variants."

Over time researchers have ramped up clinical trial infrastructure, and repeated surges of the coronavirus SARS-CoV-2 have ensured a ready pool of potential study participants. The result has been an accelerated drug pipeline, Tabak says. "It has been two years, which feels like a long time for everybody," says Paul Verdin, head of consulting and analytics at the London-based pharmaceutical analytics firm Evaluate. "But in the grand scheme of drug development, that's not very long."

TRICKLE BECOMES FLOOD

Early in the pandemic, much research focused on finding ways to treat people who were seriously ill with COVID, to save lives and ease pressures on hospitals. In mid-2020 scientists found that a steroid called dexamethasone tamps down supercharged immune responses that can contribute to late stages of severe disease and reduces deaths in people in this group. Such steroids remain the most effective treatments for reducing COVID deaths.

Other drugs target the virus more directly but must be administered by medical professionals, limiting their use. The antiviral drug remdesivir (Veklury), made by Gilead Sciences in Foster City, Calif., is given as an infusion and so was reserved, until recently, only for people hospitalized with COVID. (On January 21 the U.S. Food and Drug Administration authorized remdesivir for outpatient treatment of people who are at high risk of COVID complications.)

Several firms have developed monoclonal antibodies—mass-produced versions of the neutralizing antibodies that the immune system pumps out to bind to and disable SARS-CoV-2. These therapies offered another early route to treatment, and more than 200 monoclonal antibodies are now under development or authorized. But they are expensive compared with other treatments, are in short supply and often have to be infused. One recent exception is a long-lasting combination of two monoclo-

nal antibodies, called Evusheld. This drug, made by AstraZeneca in Cambridge, England, can be injected into muscle and was authorized by the FDA last December for prevention of COVID in people at high risk of exposure to SARS-CoV-2.

With time, the focus began to shift to drugs that could be used outside a hospital setting to treat mild illness, in the hope of preventing progression to more severe disease. In late 2021 two antiviral treatments became available as pills that could be taken at home—Lagevrio (molnupiravir), developed by Merck, based in Kenilworth, N.J., and Ridgeback Biotherapeutics in Miami, Fla., and Paxlovid (a combination of two drugs, nirmatrelvir and ritonavir), developed by Pfizer, based in New York City.

Neither drug is a panacea, notes José Carlos Menéndez Ramos, who studies pharmacy at the Complutense University of Madrid. A laboratory study has suggested that molnupiravir might be able to cause mutations in human DNA, leading regulators to advise against its use during pregnancy. Some countries, including France and India, have chosen not to authorize it. And Paxlovid's use could be limited because it might interact with a wide range of commonly used medications.

Luckily, the two could soon have company. Many antivirals in trials target one of two key viral proteins, with the aim of stopping the virus from replicating. Like molnupiravir, some of these target a protein called RNA-dependent RNA polymerase. About 40 candidates are under development, says Chengyuan Liang, who studies pharmacy at Shaanxi University of Science and Technology in Xi'an, China. Another roughly 180 molecules act like Paxlovid and block the SARS-CoV-2 main protease protein, which is responsible for clipping viral proteins into their final, functional forms. Of these protease inhibitors, the one that has progressed furthest is S-217622, made by Shionogi in Osaka, Japan, which is in late-stage clinical trials.

Other antiviral medications with a fresh set of targets are working their way along the pipeline. Some of them have been selected to block the human proteins that SARS-CoV-2 uses to infiltrate cells rather than viral proteins. For example, a cancer drug called plitidepsin targets a human protein called eEF1A, which is involved in making proteins and is important for the replication of several viral pathogens. Plitidepsin has been shown to reduce SARS-CoV-2 replication in mice and is now in phase III clinical trials.

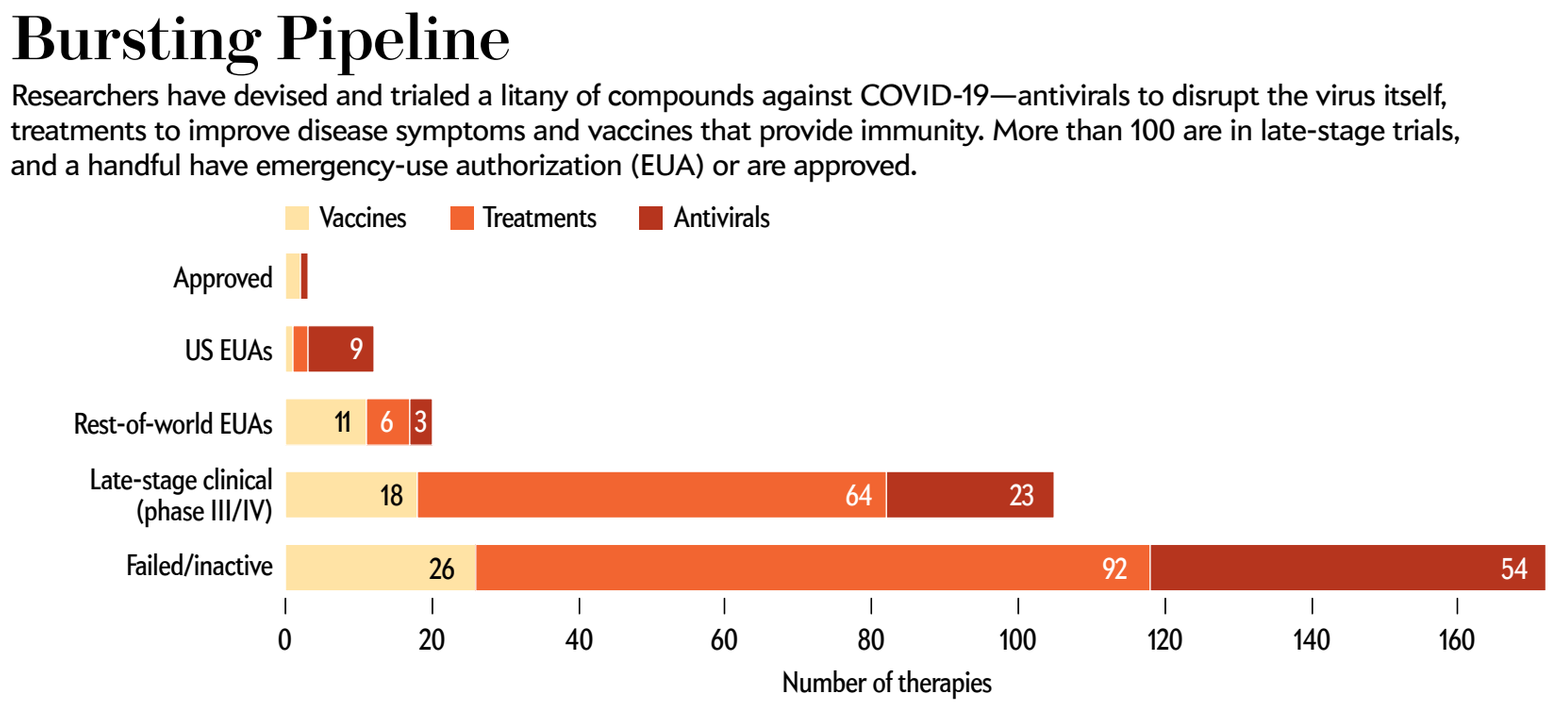
Targeting human proteins such as eEF1A could make it more difficult for the virus to mutate to evade the drug than when viral proteins are the target, Ramos says. "On the flip side, targeting a host protein can lead to toxicity," he adds. In the case of plitidepsin, Ramos is hopeful that the dose required to restrict SARS-CoV-2 replication is low enough, and treatment duration short enough, for the drug to be a safe antiviral.

Researchers hope to target a smattering of other viral and human proteins important for SARS-CoV-2 replication. For example, the drug camostat, made by Ono Pharmaceutical in Osaka, inhibits a human protease, called TMPRSS2, that SARS-CoV-2 and several other coronaviruses use to enter human cells. Camostat is already used in Japan to treat nonviral conditions such as pancreatitis.

NEW COMBINATIONS

Some familiar COVID antivirals could find fresh uses, either in a formulation that makes them easy to administer or in different patient groups. Antivirals such as remdesivir seem to work best when given earlier in the course of infection, before severe disease sets in; researchers are working on oral formulations to see whether this definitely is the case.

Conversely, researchers also want to know whether the new oral antivirals could improve outcomes for people with severe COVID. Clinical trials of molnupiravir in people who have been hospitalized have suggested that these drugs would not work against moderate or severe illness, when the immune system is contributing to the damage. But epidemiologist and infectious disease specialist Peter



"Hundreds of COVID Trials Could Provide a Deluge of New Drugs," by Heidi Ledford, in *Nature*, Vol. 603; March 3, 2022; Source: BIO COVID-19 Therapeutic Development Tracker

Horby of the University of Oxford says that the studies of people in hospitals might have been too small for researchers to draw a firm conclusion. It's a common problem during the pandemic, he says: many investigators launched quick, small trials, enrolling too few participants to yield clear answers. Some treatments were abandoned prematurely. "The studies weren't big enough, and stuff was being ditched way too early in our opinion," he says.

Horby is one of the lead scientists on the U.K. RECOVERY trial—a large, multitherapy trial in people hospitalized with COVID. RECOVERY will test molnupiravir and eventually Paxlovid, he says. Treating sicker people could be the best way to make the most of these scarce drugs. Most infected people won't develop severe disease, and there is no definitive way to tell who will; giving the drug to people with mild disease might not yield as much benefit as treating those who are severely ill. While supplies of the drugs are low, he says, "you've got to target your use of a limited and expensive resource."

The RECOVERY trial will also begin to unpick whether these antivirals work synergistically when given together. Some participants in the trial will receive one of the drugs; others might receive a combination of the two or one of the antivirals together with a monoclonal antibody. Researchers hope that combining antivirals can boost their effectiveness and reduce the chances that the virus will develop resistance to the drugs. "We don't have many antiviral options," Horby says. "If we lost any, it would be a disaster."

Researchers are exploring other options for those hospitalized with COVID. Treatments at this late stage often focus on the immune system, which, whipped into a frenzy by the viral infection, can begin to harm the body's own tissues. Anti-inflammatory drugs are top of the list. RECOVERY is now looking at higher doses of steroids such as dexamethasone, and several trials are studying whether diabetes drugs called SGLT2 inhibitors—also thought to have anti-inflammatory properties—help people with moderate to severe COVID.

A health-care worker tests samples from people with COVID-19 as part of the ANTICOV trial.

Kenny Mbala/DNDi

REUSE AND REPURPOSE

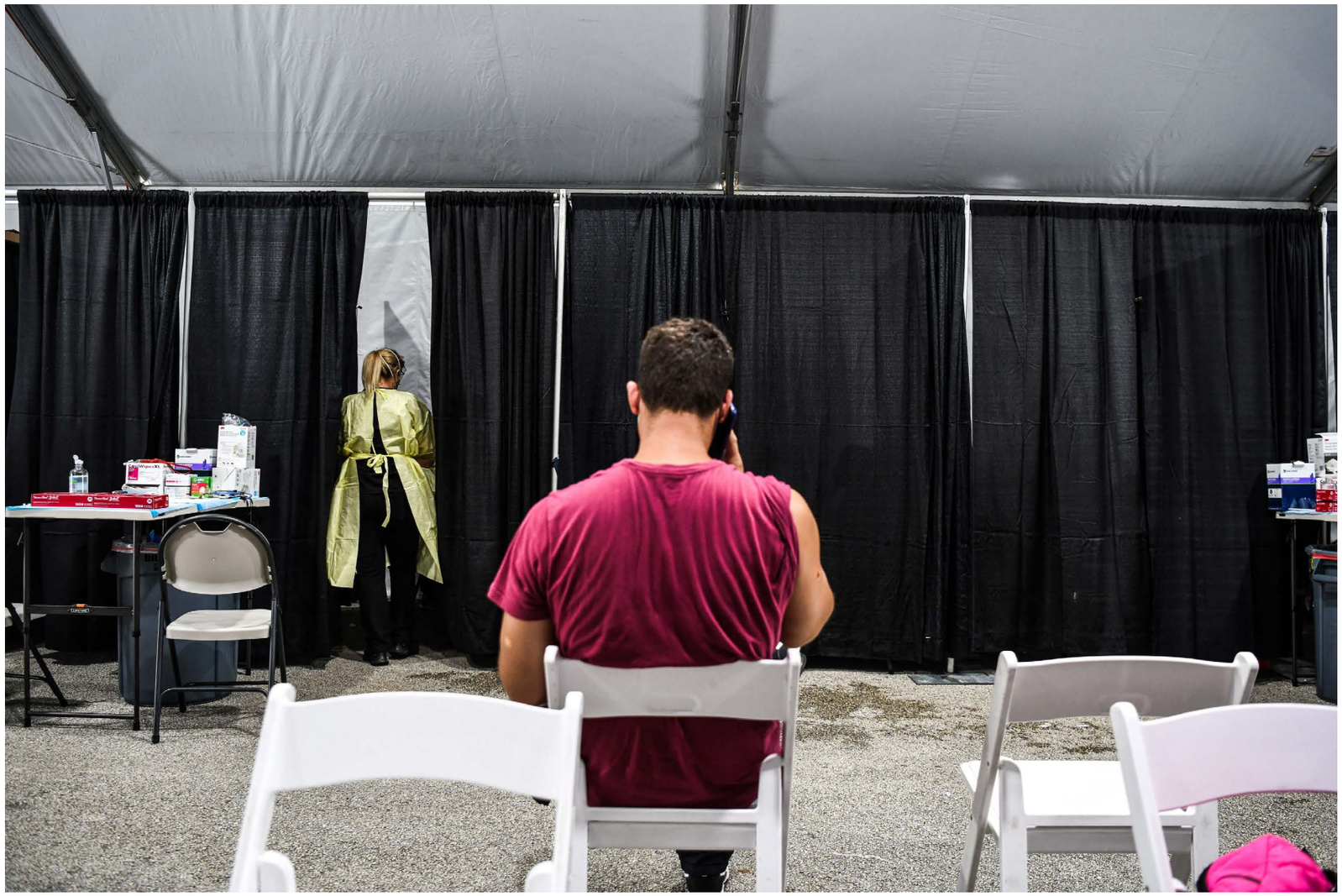
Globally, some of the most important trials are those that study widely available drugs developed to treat other diseases. For Philippe Guérin, director of the Infectious Diseases Data Observatory at the University of Oxford, it has been frustrating to see that many large clinical trials are focused on therapies that, in a lot of countries, will be too expensive to buy or too difficult to administer. "There is a clear disconnect between the needs of lower- to middle-income countries and the level of research," he says. "Most of the large funding was focused on the needs of high-income countries."

This was reflected in the early attention given to people with severe COVID, who were coming to hospitals and being treated in intensive care units. "In low-income countries, you don't have ICU capacity," Guérin says. "What you want to do is try to prevent the nonsevere patients from becoming severe, and that was not clearly the priority of the funders."

Much of the early research on treating mild COVID focused on monoclonal antibodies, notes public health specialist Borna Nyaoke, clinical operations representative for East Africa at the Drugs for Neglected Diseases initiative, a nonprofit organization in Nairobi. But these drugs pose a challenge in lower- and middle-income countries, she says, because of their cost and because they need to be stored at low temperatures and administered by trained medical personnel. And the newer, oral antivirals promise to be less expensive, although they are still in short supply.

For more practical solutions, Nyaoke looks to the ANTICOV trial, which is enrolling participants in 19 sites across 13 countries in sub-Saharan Africa. The trial is looking at a range of repurposed treatments, including the antiparasitic drug ivermectin; an inhaled steroid called budesonide; and the antidepressant fluoxetine. (Other trials, including one run by ACTIV, are testing a similar antidepressant, called fluvoxamine, which has shown promise in some early clinical trials.)

Some of these treatments have already been tested—and sometimes failed—in smaller clinical trials. Ivermectin, in particular, has become a popular but controversial COVID treatment in many countries, despite clinical trials indicating that the drug does not work as an antiviral in early stages of infection. Both ACTIV and ANTICOV are testing the treatment anew. ACTIV is running a trial in people with mild to moderate COVID, and results are due in the next few months. "No matter what we find, that will be of interest to many people," Tabak says. The ANTICOV trial will test ivermectin for its potential anti-inflammatory properties in people seriously ill with COVID and will combine it with an antimalarial drug. Preclinical data have been promising, Nyaoke says: "Combining drugs with different mechanisms of action increases a treatment's chances of success."



A patient waits for his treatment inside a monoclonal antibody treatment site in Pembroke Pines, Fla., on August 19, 2021.

Chandan Khanna/AFP via Getty Images

Drug developers still face challenges when it comes to finding COVID therapies. For instance, there is a shortage of nonhuman primates to use for research, and the costs of animals have skyrocketed, Liang says.

And although clinical trial planners are not short of participants, running a trial in a pandemic is complicated: emerging viral variants can change the spectrum of symptoms, the severity of disease and the population that is most affected. In some cases, variants have rendered COVID therapies—particularly some of the monoclonal antibodies—obsolete. In contrast, broader-acting drugs such as remdesivir, which was developed in 2015 and tested against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in animal models and against Ebola in humans, could be useful tools in future pandemics. In the middle of this chaos, it's hard to know which of the many therapies in current trials will be successful, Verdin says. "The whole thing is such a big churning bubble; the goal posts are constantly moving," he says. "It's very difficult to pick a winner."

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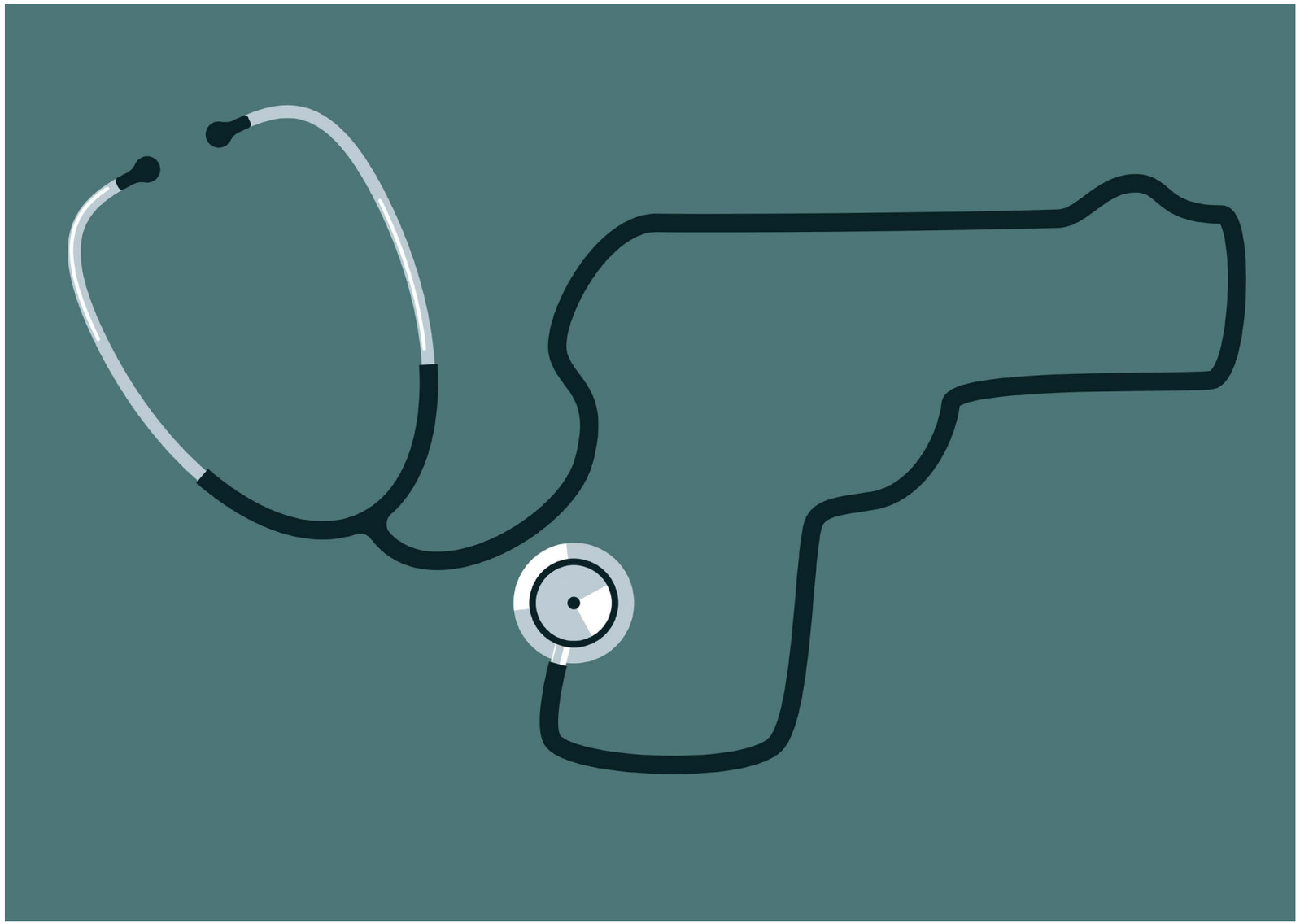
Gun Violence Is an Epidemic: Health Systems Must Step Up

There are tools that hospitals can use to reduce the number of firearm injuries that come through the doors. We are piloting one such project



Boris Zhitkov/Getty Images

The rate of gun violence continues to rise across America. There was nearly a 30 percent increase in homicides between 2019 and 2020, making it the largest one-year increase in six decades. The number of gun deaths in 2021 climbed even higher and is approaching the previous peaks in gun death rates in the early 1970s and early 1990s. Although the severe disruption of the COVID-19 pandemic has clearly played a role, we may not fully understand for years what has caused this increase.

In the meantime, health systems must play a larger role in preventing gun violence. We understand that this pandemic has pushed our health-care system to its limit, and prioritizing anything but immediate needs will be difficult, but gun violence is one of America's deadliest and longest-running epidemics. It is nothing less than an immediate need.

Last summer Northwell Health, where the authors are, respectively, CEO (Dowling) and pediatric trauma surgeon (Sathya), asked several dozen medical centers to work together to ask Congress to better fund gun violence screening programs. Eighteen systems joined us, but they make up only 3 percent of the nation's medical centers. We can do better.

We are calling on health-care systems across

the country to build on proven hospital-based violence intervention (HVIP) models to create coordinated, systemwide programs that give doctors, nurses, physician assistants and social workers the tools they need to talk with the people they treat about preventing gun injuries.

To that end, Northwell Health established a Center for Gun Violence Prevention (CGVP) in 2019. The center coordinates our efforts to make gun violence a top health-care priority across our system by conducting research on HVIP strategies, developing a public health strategy to combat this epidemic, leading a peer-to-peer Learning Collaborative to share best practices, and advocating for evidence-based GVP reforms on a local, state and national level.

Our work is cut out for us, but we have a framework with proven results.

The first HVIP, Caught in the Crossfire, was launched in 1993 in Oakland, Calif., to offer wraparound mentoring, legal, employment and mental health supports to young people who are in the hospital recovering from a gun injury. Researchers at the University of San Francisco Medical Center evaluated the program and found that participants were 70 percent less likely to be arrested for any offense and 60 percent less likely to be involved in any criminal activity, compared with a control group who did not receive the program's services. Participants in another gun violence intervention program at the University of Maryland Medical Center were far less likely to be shot again; only 5 percent of those in the program were reinjured, compared with 36 percent who were not in the program.

More than 90 percent of adults who live in homes with guns say they have never discussed firearm safety with a clinician; in an effort to lower that figure, Northwell is conducting a first-of-its-kind National Institutes of Health–funded study. We are currently piloting a universal screening protocol where we ask our patients questions about their exposure to firearms to better understand their risk of being on one end of gun violence or the other.

For the pilot, providers in our health system talk to patients who comes into three of our hospitals about how to avoid gun injuries—the same way we talk to them about sugar intake, exercise or motor vehicle safety. Previously there was no standardized procedure for when and how clinicians should have these conversations. We now talk to patients who have access to firearms about safe storage, provide them with gun locks and connect those at risk of gun violence with appropriate intervention services—such as peer mentors, mental health support, job training programs, and more.

In urban settings, up to 41 percent of people treated for violent injury return to the emergency room with a gunshot wound. Hospital-based violence intervention can only succeed when it is closely linked with organizations working to do violence interruption and street outreach. That close coordination requires time, money and relationship building, not just between doctors and nurses, law enforcement and violence interrupters but also between senior leaders at hospitals, police departments and community-based organizations.

The Biden administration seems to appreciate the scope of this other epidemic. The American Rescue Plan Act, a COVID relief plan, includes $350 billion for states and local governments. Many of them are using some of that funding to support violence intervention programs. And if the federal government enacts legislation along the lines of President Joe Biden's Build Back Better framework, an additional $5 billion would be dedicated solely to hospital- and community-based violence intervention programs, which would be the largest investment in gun violence prevention in American history.

Finally, while making changes within our hospitals and our industry is important, the best way to help reduce gun violence in the long run is to push policy makers to act. When alerted to the health detriments of tobacco and the need for better motor vehicle safety laws, our government has responded. While our lawmakers legislate climate change and reproductive justice, both of which affect the people who walk through our doors, they must also be frank and realistic about the toll of gun violence and their power to mitigate it.

Health-care institutions can only do so much to protect the people we serve. But we account for 17 percent of GDP and 22 million jobs. This is why the 600 or so health systems in the U.S. and the executives that run them must combine our voices and industry resources to advocate for commonsense gun reforms at every level of government.

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 the book *Runaway Medicine: What You Don't Know May Kill You*, which was recently Amazon's number-one Hot New Release in Health Care Administration. She received her M.D. at the Johns Hopkins University School of Medicine.

When Is It Safe to Have Sex after COVID?

How to limit your risk of transmitting or getting infected with SARS-CoV-2

Recently my husband endured a mild case of COVID—a cough, a sore throat, some aches and fatigue. Fortunately, he is vaccinated and boosted, and he recovered quickly. On day 10 after infection, he produced a negative rapid antigen test. Cool! So when can we have sex?

This, it turns out, is a more complicated question than it might appear. And although Omicron appears to be loosening its grip on the U.S., the virus is nowhere near done with us, meaning plenty of people will be asking the same question in the weeks and months to come.

We know that SARS-CoV-2, the coronavirus that causes COVID, is spread mostly through the air—that is, by people breathing in infectious aerosols or respiratory droplets that are produced when someone speaks, coughs, sneezes or breathes (or breathes heavily).

Maria Voronovich/Getty Images

Close contact could get tricky pretty fast for those hoping to resume their sex lives immediately after a COVID bout. The close contact that comes with intimacy or kissing can place you at higher risk of catching the virus if your significant other is infected—even if they are asymptomatic. The coronavirus can spread with close heavy breathing or contact with saliva. This much is understood. But in terms of intercourse itself, what do we really know?

First, there is no evidence that COVID-19 is a sexually transmitted disease (STD). While the coronavirus is primarily spread through respiratory fluids, STDs are mostly spread through contact with other body fluids: semen, vaginal secretions, blood, and so on.

Bits of the viral genome have been detected in semen from small groups of COVID patients in studies using polymerase chain reaction (PCR) assays. Further methods to identify whether infectious virus is present—growing it in the laboratory or seeing if the virus is trying to copy itself—have so far yielded negative results, says A. J. te Velthuis, a virology and molecular biology expert at Princeton University. "So, overall, it seems that no active virus is present in the testes/prostate. The same is true for vaginal excretions."

Two small studies of women with severe COVID did not find the virus detectable in vaginal fluids, and another study of 12 pregnant women with confirmed COVID infection did not either. Nelson Bennett, a urologist at the Northwestern University School of Medicine, and Justin Dubin, a urology fellow specializing in male sexual medicine and infertility at the Northwestern University School of Medicine, both say that while they hope to see more research in this area, the risk of transmitting COVID via sexual activity is "very low."

The virus has been detected in stool samples of patients with COVID, and more studies are needed to determine whether one might spread the virus during anal sex or such sexual activities as rimming (placing the mouth on the anus).

Even after 10 days and even after vaccination, "there is some risk of viral transmission via air or saliva," te Velthuis says. But if you've tested negative after a lateral flow assay—a rapid antigen test—that risk is limited, and "sexual activity should then also be no problem," he adds.

Now, keep in mind some common sense: Safe sex is certainly recommended. The Centers for Disease Control and Prevention cautions that a negative antigen test "does not necessarily indicate the absence of transmissible virus."

If your partner or you are in isolation, have a known exposure or are experiencing typical COVID symptoms, you shouldn't have sex. If someone has just had COVID, Bennett suggests taking a rapid test, and Dubin adds, "It isn't the sex that will get you COVID but everything else that leads up to it. Sharing smaller closed spaces, being in close contact, kissing—these are all much more risky behaviors for infection than the sex itself."

According to NASTAD, the National Coalition of STD Directors, you should make sure three things have happened after you have recovered from COVID before you resume sexual activity with a household partner: no fever for three days without the use of fever-reducing medications; improvement of other symptoms; and the passage of 10 days since your symptoms began.

Michael Mina, an expert on rapid tests and chief science officer at EMed, says that if you had COVID but then posted two negative rapid tests 24 hours apart, you're "very, very unlikely" to pass the virus either through kissing or by having sex. "I'd argue it is not even necessary to wait the full 10 days," Mina says.

Amid the uncertainty, the safest partner is you. Masturbation does not spread COVID and thus is very safe. And rates of masturbation have increased during the pandemic, according to Susan Milstein, co-author of *Human Sexuality: Making Informed Decisions*. If you're having sex with someone who does not live with you, you may not know what precautions that person has been taking, and asymptomatic spread can occur. For obvious reasons, intimacy with multiple partners can contribute to the spread of COVID.

Video dates, sexting, erotic phone conversations and online chat rooms are all noncontact options. With respect to physical contact outside the home, it's all about precautions. "Sex is sex. It's going to happen," says Dianne Rosenberg, a retired obstetrics and gynecology physician. "Have a glass of wine together while checking a rapid test and wear a condom."

Although some recommendations may seem impractical, experts have suggested measures that will likely reduce your risk of contracting COVID or sexually transmitted infections during

sex. Using condoms, avoiding or limiting kissing, continuing masking, washing sex toys before and after use—these may all make a difference. So may reducing the number of sexual partners, choosing positions that limit face-to-face contact, keeping windows open and improving ventilation. Prior to and after sex, washing your hands and body with soap and water is a good idea.

And of course, getting vaccinated and boosted, as well as masking in public spaces, remain priorities. Not only do they help control the pandemic, but they are safe-sex precautions in their own right.

People who have weakened immune systems or are at high risk of severe COVID—those with diabetes, cancer or lung disease, for example—might consider abstaining from sex with people outside their household, taking extra precautions and checking with their physicians.

Safe sex during a pandemic means considering what your partner's vaccination status is, what changes work best for both of you and what you each need from sex—and sharing that information with each other. Like so many facets of COVID, we still have much to learn. But even for those who've contracted the virus, it's mostly good news.

And it is needed. "Sexual health is just as important as a functioning heart, mental health and all other aspects of physical health," says Jessica Kingston, an obstetrics and gynecology physician at U.C. San Diego Health. In the midst of a global pandemic, anything that brings us such pleasure or joy is well worth a few precautions.

Ashley Andreou is a medical student at Georgetown University.

Anti-Trans Laws Will Have a Chilling Effect on Medicine

I am a future psychiatrist hoping to care for transgender people. But I fear these laws will make it difficult to do so

Transgender rights advocates hold pride flags during a rally against Ohio legislation banning transgender women from female sports in June 2021 in Columbus, Ohio.

Stephen Zenner/SOPA Images/LightRocket via Getty Images

On Transgender Day of Visibility—March 31—we should be celebrating the accomplishments, honoring the resilience and advocating loudly for the rights of people who are trans. Yet the growing onslaught of anti-trans legislation targeting the health-care decisions that families make with their doctors threatens to cast a shadow over this day.

About a year ago I lost a family member to the mental trauma of transgender discrimination, so I speak from a place of watching someone I love suffer from lack of support. These recent and proposed laws, none of which are grounded in evidence-based medicine, will affect the mental and physical health of adults and children and the families who support them.

I am in medical school, and I plan to specialize in psychiatry with the hope of working with people who are transgender or nonbinary. Instead of making me feel empowered to serve, the intent behind these laws makes me fearful for my future patients. The directive in Texas that calls gender-affirming health care "child abuse" makes me afraid to practice and outraged that any state can insert itself into the clinical decision-making that we spend thousands of hours honing over several years. There are so few doctors who treat people who are transgender, let alone specialize in the physical and mental medicine specific to their needs. These laws could dissuade clinicians from entering this line of work.

Instead of enacting laws that deny the basic

health rights of the trans community—and signal to trans individuals that they are not safe, accepted or supported—policy makers, clinicians and advocates need to work together to create laws that counteract and prevent the health disparities that are exacerbated by the enduring discrimination of this community.

One of the biggest points of misinformation in the lobbying for these laws is what constitutes gender-affirming health care. Gender-affirming care is defined as treatments that delay the onset of physical changes associated with puberty and ones that create physiological and physical changes that affirm one's gender identity (for example, hormone therapy or surgery). It's important to note that transitioning is a spectrum—not everyone who is transgender chooses hormone therapy, and not everyone chooses surgery. Yet all options are at stake with some of the laws that have passed or been proposed.

Doctors do not offer gender-affirming therapy rashly, and they only prescribe puberty blockers after working with a younger transgender person considering transition for a long time. Access to puberty blockers is critical because puberty's effects on certain body parts cannot be easily reversed by hormone therapy later in life (for example, testosterone's effects on voice). Altogether, the process requires coordinated counseling and medical oversight from a multidisciplinary clinical team that can include psychiatrists, endocrinologists and urologists, among others.

About 25 percent of transgender and nonbinary people choose gender-affirming surgery. Medical guidelines do not recommend surgery (such as facial reconstruction, mastectomy or phalloplasty) until a person is 18 years old, a point purposefully misrepresented by politicians who falsely say doctors are operating on young children.

"I guarantee you, if this bill passes, children will die. And I will call you guys every single time one does."
—Michele Hutchinson

More than 58,000 transgender teenagers who are transitioning are at risk of losing access to their medical care, according to a report from the University of California, Los Angeles, School of Law's Williams Institute. The effects of these bills and laws would be devastating. A large survey published in *Pediatrics* in 2018 found that 30 to 50 percent of young trans and nonbinary people reported a previous suicide attempt, compared with fewer than 9 percent of all adolescents. Experts hypothesize that this greater risk among trans youth is linked to internalized rejection and shame.

In contrast, transgender youth who are supported by their families and receive gender-affirming care have markedly lower rates of depression: gender-affirming care has been associated with a nearly 40 percent reduction in depression and in attempting suicide in the past year. Furthermore, trans youth who have access to puberty suppressants have a much lower risk of lifetime suicide as adults.

As Texas's legislature debated anti-trans bills last year, the Trevor Project, an organization focused on LGBTQIA+ youth suicide prevention, received more than 10,800 total crisis contacts. Transgender or nonbinary youth made up more than 3,900 of those crisis contacts, and many of them reported feeling stressed, turning to self-harm and considering suicide as a result of the anti-LGBTQIA+ laws proposed by politicians in their state. Between 2020 and 2021 the Trevor Project recorded a 150 percent increase in LGBTQIA+ youth in Texas contacting the organization in crisis and seeking support. As a future psychiatrist, I find it incomprehensible that state lawmakers would willfully harm the mental health of so many young people.

All this legislation is at direct odds with the medical guidance of the American Psychiatric Association, the American Medical Association (AMA) and the American Academy of Pediatrics (AAP). These medical organizations recommend these medications and procedures for transgender individuals because there is a corpus of scientific literature affirming their benefits when medically indicated. These treatments are far from new and untested: puberty blockers have been used in medical care since the 1990s.

Calling me a child abuser will not stop my future patients from seeking care. Similar to the effects of efforts to stop abortion, transgender people and their families are liable to turn to unregulated black market products outside of the

purview of the Food and Drug Administration's monitoring of hormone product safety and quality. I can't fulfill the Hippocratic oath knowing that my inability to provide gender-affirming care might force patients into unsafe situations.

Numerous bills go on to propose criminalizing physicians if they provide hormone therapy to patients. In medical school, we had lectures on the importance of providing gender-affirming care, as well as panels specifically on the health-care experiences of transgender patients. The closure of Texas's only multidisciplinary clinic for transgender youth, GENECIS, in response to pressure from the governor is evidence of the stifling effect these laws are already having on medical professionals.

As highlighted by the pandemic, a dangerous risk factor for burnout among physicians is when they cannot control the health outcomes of their patients. Yet these bills go one step further, creating preventable negative health outcomes, and would introduce a new level of powerlessness and morale loss among providers. The AMA and AAP have both issued statements opposing recent anti-trans bills.

When speaking out against an anti-trans bill in Arkansas last year, Michele Hutchinson, a pediatrician at Arkansas Children's Hospital said, "I guarantee you, if this bill passes, children will die. And I will call you guys every single time one does." In April 2021 that anti-trans bill passed.

The day when police came to my house to tell my family that my uncle was found dead from an overdose after years of struggling with her identity, I felt like I was living through a nightmare.

In the painful days after, I committed myself to partnering with transgender communities to provide medical care and advocacy. Yet as legislators continue to signal that they would rather see people like my uncle dead than happy, alive and thriving, my grief has not subsided. Reading Texas Governor Greg Abbott's letter declaring gender-affirmative care "child abuse" and understanding that a growing number of legislators seek to bar me and other physicians from providing lifesaving care, I know my family's nightmare hasn't ended.

Despite these legal battles underscoring the transgender community's perseverance in the face of harrowing challenges, suffering is not what Transgender Day of Visibility is about. Unfortunately, brazen and medically uninformed politicians denying basic human rights over binary ideas of gender have left us no choice but to rally and continue to fight. My uncle, who was a transgender woman but liked being called "uncle," deserved more in life. This is what I can do for her in death.

IF YOU NEED HELP

If you or someone you know is struggling or having thoughts of suicide, help is available. Call the National Suicide Prevention Lifeline at 1-800-273-8255 (TALK), use the online Lifeline Chat or contact the Crisis Text Line by texting TALK to 741741.

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 the book *Runaway Medicine: What You Don't Know May Kill You*, which was recently Amazon's number-one Hot New Release in Health Care Administration. She received her M.D. at the Johns Hopkins University School of Medicine.

New Cases of Childhood Diabetes Rose during the Pandemic

It isn't clear why, but researchers are investigating a possible COVID link

Allchonok/Getty Images

The little girl felt poorly, but both she and her mom thought they knew the reason. Aliyah Davis, just nine years old, was battling COVID. Fatigued, repeatedly sick to her stomach, with no sense of smell or taste and some shortness of breath, she seemed to have a near-textbook case of the virus.

Aliyah had a history of asthma, so her mother, Christina Ortiz, took her to the emergency room, where she was told the symptoms were likely COVID-related. But two and a half weeks later Aliyah became sick again in the middle of the night, and Christina noted that her daughter had been having insatiable thirst and frequent urination ever since that first ER visit. This time a urine dip tested positive for ketones. Further workup revealed the issue: Aliyah had new-onset diabetes.

Her diagnosis in the summer of 2020 was the front edge of what has become a troubling and at times baffling development. Although researchers are still straining to understand why, it appears that COVID and diabetes have formed an intricate—and dangerous—partnership.

It's also a bidirectional one, says Francesco Rubino, a pioneer in diabetes surgery at King's College in London. "The relationship appears not just one way but two ways," Rubino tells me.

On one side, diabetes is a key risk factor for developing serious illness or dying after catching COVID. But we now also have multiple reports of patients who contract COVID and then go on to

develop new-onset diabetes and sometimes severe imbalances in their blood sugar (glucose), such as diabetic ketoacidosis (DKA). In fact, a large diabetes study of adults published recently in the journal *Lancet Diabetes and Endocrinology* showed that individuals who recovered from COVID over the past year stood a 40 percent greater chance of receiving a new diabetes diagnosis than the uninfected.

At this point, evidence is more limited in children, and there is much that we do not know. "While we are concerned that COVID might cause diabetes, we need to rule out other reasonable causes of this association that [are] not necessarily the one that links the virus to the disease," Rubino says.

Aliyah's blood sugar was sky-high despite having no immediate family history of diabetes, not being overweight and not having other obvious comorbidities. Her DKA diagnosis prompted a four-day hospital admission. Such a diagnosis, too, is becoming more common.

Hospitalizations in children hit record highs during the surge of the Omicron variant of the SARS-CoV-2 virus. As of March 31, more than 12.8 million total pediatric COVID cases had been reported in the U.S. since the start of the pandemic. Comparatively few children are hospitalized for COVID, but even a small percentage of a large number can be significant.

A new diabetes diagnosis is a serious concern with the potential to change a person's life. As a chronic condition, it affects how the body uses blood sugar, and it can wreak havoc years down the line. Possible complications include kidney failure, heart attacks, stroke, nerve damage, macular degeneration, blindness, vascular issues and even amputations.

With type 1 diabetes, which is usually diagnosed in children and young adults, it's thought that one's own immune system mistakenly attacks insulin-producing cells in the pancreas, so that the body makes little or no insulin and blood sugar levels rise. With type 2, primarily diagnosed in adulthood and far more common, one's cells become resistant to insulin, leading to similar spikes in blood sugar levels. New-onset cases of both types have been reported during the pandemic, says Rubino, co-principal investigator of CoviDIAB, a global registry which is collecting detailed information on the topic.

Researchers at the Centers for Disease Control and Prevention, analyzing two large insurance claim databases of those under age 18, found that children with a prior COVID infection were 31 percent to 166 percent more likely to develop diabetes than those who hadn't had COVID (or who had a different, non-SARS-CoV-2 respiratory infection). Compared with those other acute respiratory infections in particular, a new diabetes diagnosis was 116 percent more likely to occur in those who had a COVID infection.

One of the earliest reports of this development came from London in 2020, where researchers found an 80 percent increase in new-onset type 1 diabetes in children during the pandemic. A study at Rady Children's Hospital in San Diego, meanwhile, noted a 57 percent increase in children admitted with new-onset type 1 diabetes during the pandemic from March 2020 to March 2021. This study also found a higher percentage of children who presented with DKA, indicating a greater severity of disease at the time of diagnosis, according to Jane Kim, a study author and pediatric endocrinologist at the University of California, San Diego.

Reports of increasing diabetes rates in children are "in line" with several emerging observations internationally, says Paolo Fiorina, a diabetes expert and research associate at Boston Children's Hospital–Harvard Medical School. Finnish, Romanian, Italian, German and Australian researchers all have found that more children were diagnosed with new-onset type 1 diabetes during the pandemic than before the pandemic. At Children's Medical Center in Dallas, pediatric endocrinologist Abha Choudhary says that type 2 cases are rising, and "these patients are sicker at presentation."

"I do believe that COVID-19 is causing a surge" in new diabetes cases, Fiorina says. "This is clearly demonstrated now … and it's much higher than what is observed in other viral infections such as SARS-CoV-1 and hepatitis." Others, including Rubino, are cautious about attributing causation. "For the moment we can say that there is an association between new-onset cases of diabetes and COVID-19," he says. "I think that's pretty solid." (The American Diabetes Association says a direct link is not yet clear.)

Researchers are still trying to learn the mechanisms behind a potential link. Also, the long-term

connection between SARS-CoV-2 and diabetes is not well established. For that matter, type 1 and type 2 diabetes are different disease processes, Kim says. “We want to be careful in extrapolating findings from type 1 [to] type 2, and vice versa,” she says.

It’s possible, experts say, that the pandemic’s effect on our health-care systems is playing a role here. Previous delays in seeking care, for example, might justify some of the increases in new diabetes cases. Rubino asks, “Is this truly new diabetes or just newly diagnosed but preexisting diabetes?”

Some scientists theorize that COVID might lead to diabetes through a direct attack of pancreatic cells. Research has shown that the coronavirus can infect insulin-producing cells in the pancreas, the so-called beta cells. Autopsy results of COVID victims have confirmed viral antigen presence and even damage to some of these beta cells.

“When New York City was in the center of the pandemic in April 2020, we learned that it was very challenging to control the blood glucose level of some COVID-19 patients,” says Shuibing Chen, director of the diabetes program at Weill Cornell Medical College and an NIH-funded team researching the issue. “Then we tested different cells for their permissiveness to SARS-CoV-2. Very surprisingly, we found pancreatic beta cells can be infected.” Those cells appeared to have been transformed in the process, rendering them incapable of functioning properly.

Another NIH-funded team, this one led by Peter Jackson of the Stanford University School of Medicine, employed mass spectrometry to see that beta cells “were strongly reprogrammed by the virus to cause cell death,” Jackson says. That process, he says, could lead to new diabetes in some patients or a worsening of the condition in others. “The effects we see in vitro are so strong,” he adds.

And researchers are considering other possibilities. It has long been known that with severe illness or infection, a stress response in the body can lead to high blood glucose, called hyperglycemia. The virus might also induce a cytokine storm—a whirlwind of inflammation and an overzealous immune response—that could lead to insulin resistance and beta cell dysfunction or incite an autoimmune reaction, in which one’s own defense system attacks the pancreas and makes it dysfunctional.

Another potential factor: “Children have gained weight during the COVID pandemic, likely because of lack of exercise, increased food intake and psychosocial stress,” Choudhary says. That could boost childhood obesity, which is associated with a higher risk of developing type 2 diabetes. Some patients also may have had prediabetes, which occurs in one in five adolescents, according to the CDC. In susceptible individuals, it is possible that the infection tips the scale enough that they develop diabetes. “Viral infections can potentially be a trigger in a patient who has a predisposition,” Choudhary says.

It’s a rather exhaustive list of possibilities—even steroid medications used to treat COVID temporarily raise blood sugar levels—but vaccination rates are a part of the equation. Fiorina says that some parents’ reluctance to vaccinate their children may factor into this surge of pediatric diabetes cases, “reinforced by their incorrect thoughts that there is an evident cut-off at which younger ages mitigate increased COVID risks.” Adds Kim, “As a physician dedicated to the health of all children regardless of whether they have diabetes or not, I recommend vaccination against COVID-19 and influenza for those who do not have contraindications.”

The vast majority of people who get COVID will not develop diabetes, Rubino says, and that context is important. But with treatments mostly unavailable and researchers still trying to understand the underlying causes, families need to stay vigilant and be aware of the symptoms on behalf of their children. Constant thirst, increased urination, extreme fatigue and unexpected weight loss are particular red flags.

And positive life changes can make a big difference. Since her hospitalization, Aliyah, now 11, is doing much better. She is on an insulin regimen, and she and her mother carefully monitor what she eats. While a vaccine wasn’t available when she contracted the virus, she is now fully vaccinated, her mom says.

She is also back to doing what other children her age are doing, “playing with my friends,” Aliyah says. Considering the difficult journey she has made, that is a small joy not to be underestimated.

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The Federal Government Should Decriminalize Marijuana

An ideal federal marijuana policy would reduce arrests, while supporting a highly regulated marketplace

In April the U.S. House of Representatives narrowly passed a bill called the Marijuana Opportunity Reinvestment and Expungement (MORE) Act. The bill would remove marijuana from the federal government's list of illegal substances, a first of many steps in the process of decriminalizing the drug nationally. The bill would not create a nationwide legal cannabis market (as some headlines have implied) or remove any individual state's criminal penalties; additional federal legislation would be required to accomplish those goals.

Public opinion has swung rapidly in favor of legalization, and there is growing discontent among the public and policy makers with the

Representative Barbara Lee of California speaks as House Judiciary Committee Chair Jerrold Nadler of New York (*right*), Representative Pramila Jayapal of Washington (*center*) and Representative Steve Cohen of Tennessee (*left*) look on during a news conference, on Capitol Hill to highlight the Marijuana Opportunity Reinvestment and Expungement (MORE) Act legislation in Washington, D.C., on November 19, 2019.

Olivier Douliery/AFP via Getty Images

criminalization of low-level drug offenses. Lawmakers and legalization advocates will likely continue to propose policies to legalize marijuana at the state and federal levels. As public health researchers who have studied policies regulating marijuana, alcohol and tobacco, we are strongly in favor of decriminalization, though cautious about full legalization. The continued criminalization of marijuana harms people, but the history of legal alcohol and tobacco shows that public health can suffer when profits take priority over the public good. Here is what we think an ideal federal cannabis policy might look like, taking into account three primary considerations: just and equitable criminal policy, individual liberty and strong regulation.

Decriminalizing marijuana and legalizing it are two separate policy questions. Our research has shown that they can have different outcomes. From 1970s into the 2000s, possession of cannabis was a misdemeanor in most states, carrying the possibility of large fines and criminal records for having even small amounts of the drug. We and others have long thought these penalties are disproportionate to the crime.

In 2008 Massachusetts reduced penalties such that possession of small amounts of marijuana became akin to a traffic ticket. Many other states followed. This is decriminalization of marijuana: fewer or lesser penalties, though not necessarily with laws or infrastructure supporting legal sales. People of color are much more likely to be arrested for possession than white people, and this disparity has worsened in states that have not decriminalized or legalized cannabis. For these reasons, public health advocates have become more vocal in calls for cannabis decriminalization because there are health effects of being arrested or having a criminal record. For example, the American Academy of Pediatrics issued a policy statement in 2015 calling for marijuana decriminalization in light of consequences such as lost job and educational opportunities and trauma associated with arrest and detainment.

Yet legalization doesn't completely solve the criminalization problem, because people can still break the law through underage possession, illegal sales and other violations. Our research has shown two interesting things: in states that have decriminalized marijuana and have age-restricted legal cannabis markets, there was no immediate reduction in arrests for people under the age of 21, but in states that decriminalized cannabis possession but did not fully legalize it, there was a reduction in arrest rates of minors and enforcement disparities.

We don't yet know why this is, but perhaps in states where decriminalization was the primary goal, legislators focused explicitly on criminal penalties and carefully developed legislation that had maximum impact on criminal consequences for all ages. And in states where legislators' primary goal was creating a legal market for marijuana, the decriminalization side of the equation didn't get the same attention to detail.

Still, poor people and minorities bear the brunt of civil penalties and fines, even if there is no arrest record to go along with them. To combat this, we think that states should remove all penalties for carrying small amounts of cannabis, essentially legalizing possession for personal use but not sales or distribution. We also think states should expunge the past criminal records of people who were convicted of possession of small amounts of marijuana and even for low-level sales.

Our current drug policy regarding marijuana, when compared with laws for alcohol and tobacco, makes little sense. Cannabis rarely ever kills someone, unlike alcohol and other drugs. And deaths from the latter two are rising. We think that the individual choice and freedom that stem from a more liberal cannabis policy can contribute to the common good. Research from Uruguay, Canada and the U.S. suggests that the age-restricted legalization of marijuana sales does not lead to large increases in cannabis use among youth, a primary concern expressed by prohibition advocates. Some of this research has found that adults use marijuana more, but this is expected; the laws provide legal access to adults who chose to consume it.

Increased freedom for the cannabis industry is not necessarily a good in and of itself; however. Cannabis is an addictive substance. At its extreme, laissez-faire legalization with few regulations is harmful. History offers multiple examples of the societal harm that stems from lax regulation, including the tobacco industry, an increasingly deregulated alcohol industry and too few restrictions on pharmaceutical marketing of opioids.

As with alcohol and other drugs, a small percentage of users consume most of the

cannabis produced. These will be the marketing targets of the cannabis industry to expand sales and increase profits. Although heavy use is not known to lead to death or organ damage, there is little question that cannabis has acute effects on learning and memory and therefore on overall functioning and productivity. Over time these effects can adversely impact employment and educational outcomes, which in turn worsen health and decrease life expectancy.

Our read of the current cannabis legalization research is that most study results are consistent with the "commercialization hypothesis" put forth by policy analysts Robert MacCoun and Peter Reuter and supported by their studies of the Dutch experience with partial legalization. They argue that the removal of criminal penalties and strictly regulated sales are unlikely to lead to large increases in problematic cannabis use but that conspicuous advertising and aggressive marketing likely will.

As the U.S. Senate considers the MORE Act, we urge policy makers to be as proactive as possible in alleviating the suffering caused by unnecessary and ineffective criminal penalties for marijuana violations. We urge policy makers to consider how to limit the power and influence of an industry that will inevitably argue against taxes, restrictions on advertising and promotion, and a purchase age of 21. Decades of research show that these are the tools that can reduce the harms associated with addicting substances. Failure to use them will result in a new addiction industry in the U.S.

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