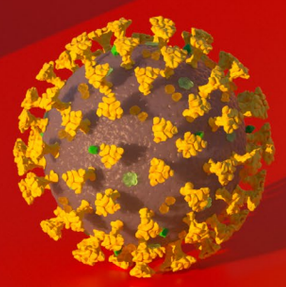
SCIENTIFIC AMERICAN
Health & Medicine

February–March 2021

The COVID Treatment Arsenal

WITH A VACCINE IN LIMITED AVAILABILITY, MANY STILL NEED MEDICINES TO KEEP THE VIRUS AT BAY



Plus:

MAGIC MUSHROOMS MAKE PROGRESS AS DEPRESSION TREATMENT

HOW TO FIX CONTACT TRACING

3-D PRINTING INSIDE THE BODY

WITH COVERAGE FROM nature

LIZ TORMES

The Remaining COVID-19 Journey

I'm sure I wasn't alone when I breathed a sigh of relief at the much ballyhooed arrival of COVID-19 vaccines at the end of 2020. We're in the midst of a dark and grief-stricken pandemic winter, and the sooner the vaccine gets us to herd immunity–and, pray, a semblance of normalcy–the better. But the well-worn trope that life is a journey, and not a destination, has an epidemiological application as well. As of this writing, the U.S. just suffered a record-breaking day of thousands of fatalities caused by the novel coronavirus. So in the interim months while most Americans wait their chance to be vaccinated, our goal certainly must be to minimize deaths from COVID-19. In this issue's cover story, Charles Schmidt takes a comprehensive look at the latest developments in clinical treatments for COVID-19 infection, many of which still need research to bolster their effectiveness (see "These Drugs Might Prevent Severe COVID").

Elsewhere on the virus beat, restrictions that have been implemented to combat the coronavirus are having a drastic impact on flu and cold rates across the globe, offering up some telling evidence for public health researchers (see "How COVID-19 Is Changing the Cold and Flu Season"). The science of viruses and human illness is ever evolving. In the case of the global pandemic, the question isn't when will we arrive at the end but how.

Andrea Gawrylewski
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Health & Medicine

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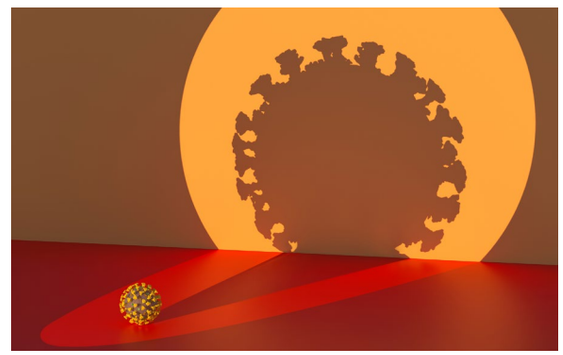

ANDRIY ONUFRIYENKO *GETTY IMAGES*

On the Cover

With a vaccine in limited availability, many still need medicines to keep the virus at bay

AL DRAGO GETTY IMAGES

WHAT'S INSIDE

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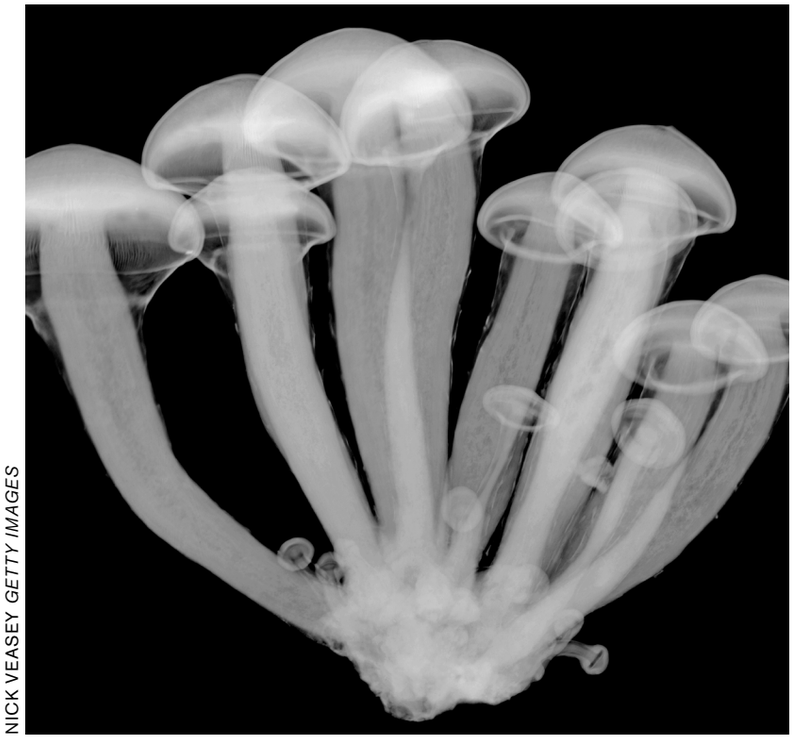

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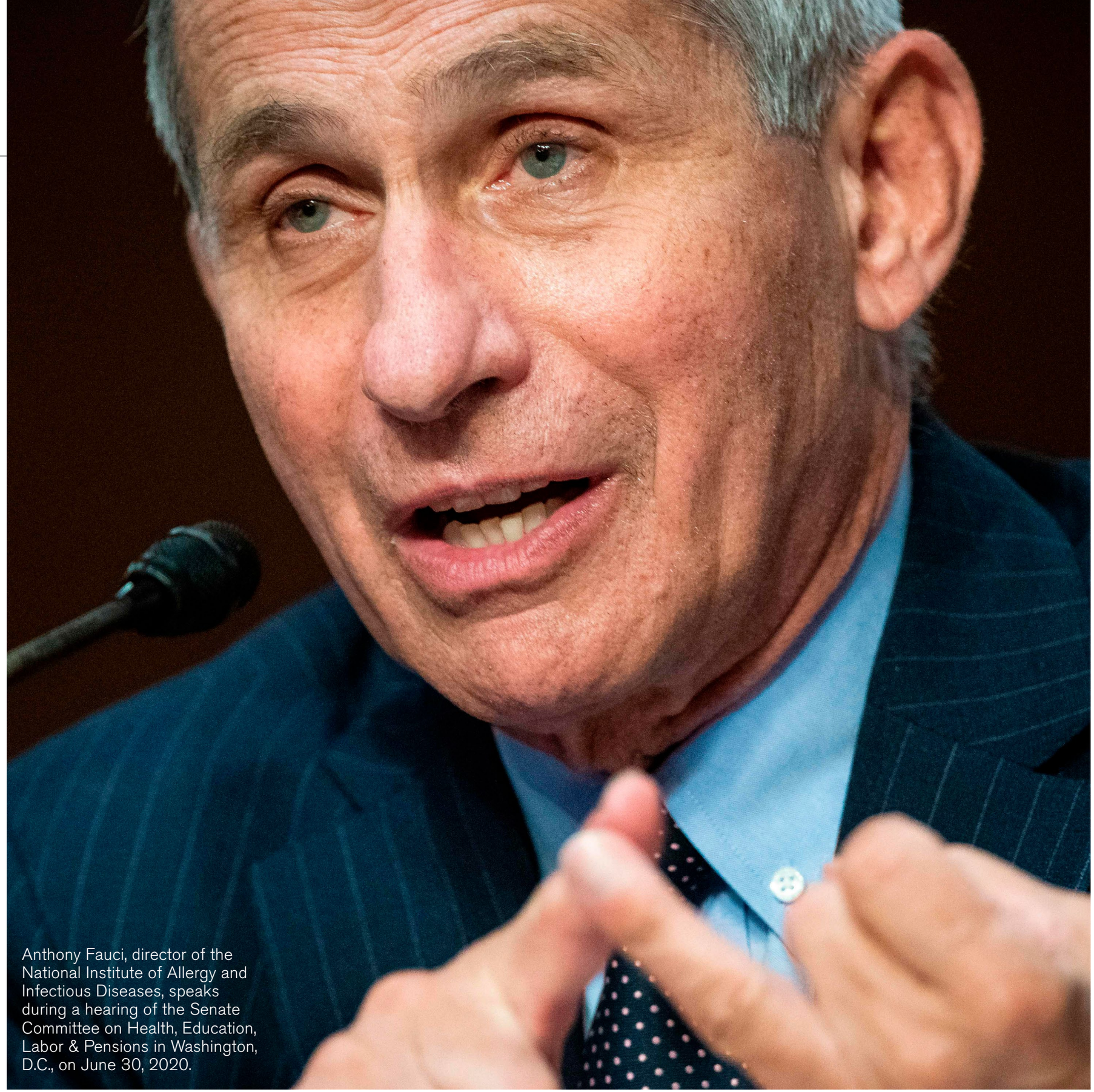
WENXIANG ZHAO

NEWS

Fauci Explains How to End the COVID Pandemic

The country's leading expert on infectious diseases shares his thoughts on resolving the current public health crisis and preparing for the next

Anthony Fauci has led the National Institute of Allergy and Infectious Diseases for 36 years and has helped guide responses to a succession of viral epidemics: HIV/AIDS, severe acute respiratory syndrome (SARS), Ebola and Zika, among others. President-elect Joe Biden recently appointed Fauci as his chief medical adviser. A voice of reason on the Trump administration's novel coronavirus task force, the physician spoke to *Scientific American* about next steps in the response to the COVID pandemic. During the discussion, Fauci highlighted an important gap in treatment options for newly infected people: more antiviral interventions



Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, speaks during a hearing of the Senate Committee on Health, Education, Labor & Pensions in Washington, D.C., on June 30, 2020.

AL DRAGO *GETTY IMAGES*

are still needed for early cases of the disease—and if successful, they could perhaps address future outbreaks that might be triggered by other emerging coronaviruses. [*An edited transcript of the interview follows.*]

Coronavirus infections are surging exponentially. Can we still get them under control?
Yes, absolutely. I've been saying this every day. If we, uniformly throughout the country, implement public health guidelines—wearing masks, keeping physically distanced, avoiding crowded situations, doing things outdoors more than indoors and washing hands frequently—I believe we will see an effect. We know from experience that the states or cities or countries that have done this have always been able to blunt and mitigate the slope of a surging curve such as this one.

What are your near-term priorities going into 2021?
They extend from what I've been talking about all along: to get the outbreak under control by uniform adherence to fundamental public health measures and to push ahead with the development and implementation of the vaccine program. I believe the vaccines that will soon become [widely] available, together with public health measures, will be the mechanism that puts this outbreak to an end.

What are your major concerns with vaccine distribution?
We hope to get the overwhelming majority of people in this country vaccinated. We have the logistics under Operation Warp Speed and General Gustave Perna [Operation Warp Speed's chief operations officer] to put vaccines into the trucks, trains, planes and whatever it is that gets them to where they need to go. But then local public health officials will need the capability and resources to distribute the vaccines in an equitable way. It's going to be a big task to vaccinate more than 300 million people—a very prodigious project.

Do you see large gatherings opening only to vaccinated people?
I don't want to make that determination now. Policy decisions will be made after we get the vaccine program going, and I will likely be part of that discussion.

Do you think drugs for early COVID will be needed now that the vaccine is coming? And if so, why?
Oh, absolutely. A lot of people will still be getting sick until we get a level of herd immunity from the vaccine to essentially eliminate this infection from society. Until then, we're going to need drugs for each and every stage of the infection: early, intermediate and late. Those types of drugs might also be used against yet another pandemic coronavirus. Remember, this is the third pandemic coronavirus we've dealt with in 18 years, starting with the SARS outbreak in 2002, then the MERS [Middle East respiratory syndrome] outbreak in 2012 and now COVID-19.

What sort of drug looks promising as a treatment for early COVID?
My overwhelming preference is for direct-acting antiviral agents that can be administered orally. We could give these drugs—likely in combination—for maybe five to six days or a week at most to completely suppress the virus. That, to me, is the highest priority.

What about a broad-spectrum agent against viral illnesses, almost like an antibiotic?
If you're talking about an antiviral that protects against all viruses, then I think that's a bridge too far. But you could get a broad-spectrum antiviral that will be good against all strains of coronaviruses and then maybe a different one that works within another family of viruses. An antiviral that worked against any manner or form of coronaviruses would be highly desirable. If we took the problem of yet another emerging pandemic coronavirus off the table, that would be a major advance.

What measures should the U.S. pursue to prevent the next pandemic?
We felt we were prepared for a pandemic before this one, and obviously, there has been a lot more suffering, infection and death than we might have anticipated. So we need to do better. We need global interconnectivity, a global health security agenda, and adequate resources and science. A part of the pandemic preparedness that was very successful—and I think we should recognize that—was the investment put into the technologies now available in the field of vaccinol-

ogy that allowed us to go from identifying a brand-new virus [around early] January to having a vaccine that's ready to administer to people in less than one year. That is a pace of scientific advance that would have been unimaginable 10 years ago. The implementation of some public health measures has obviously not been as successful.

The country has been so divided. Do you think we can overcome our differences in confronting the pandemic in 2021?
I don't have an easy answer for that because there clearly is a considerable degree of divisiveness in society. I think uniting people will be a challenge for the new administration. I hope they succeed in doing that, because when it comes to public health, everybody needs to be pulling together.

Do you have plans for a memoir once the pandemic wraps up?
[Laughs] Do I have plans for memoir? Yes, but I'm so busy right now, I can't even get a good night's sleep! So I think that's going to have to wait.

—Charles Schmidt

GETTY IMAGES

Evaluating COVID Risk on Planes, Trains and Automobiles

Stay safer on different forms of transportation

With COVID-19 reaching the most dangerous levels the U.S. has seen since the pandemic began, the country faced a problematic holiday season. Despite the risk, many people traveled using various forms of transportation that inevitably put them in relatively close contact with others. Many transit companies have established frequent cleaning routines, but evidence suggests that airborne transmission of the novel coronavirus poses a greater danger than surfaces. The virus is thought to be spread primarily by small droplets, called aerosols, that hang in the air and larger droplets that fall to the ground within six feet or so. Although no mode of public transportation is completely safe, there are some concrete ways to reduce risk, whether on an airplane, train or bus—or even in a shared car.

Airplanes

At a casual glance, air travel might seem like the perfect recipe for COVID transmission: it packs dozens of people into a confined space, often for hours at a time. But many planes have excellent high-efficiency particulate air (HEPA) filters that capture more than 99 percent of particles in the air, including microbes as SARS-CoV-2, the coronavirus that causes COVID. When their recirculation systems are operating, most commercial passenger jets bring in outside air in a top-to-bottom direction about 20 to 30 times per hours. This results in a 50–50 mix of outside and recirculated air and reduces the potential for airborne spread of a respiratory virus. Many airlines now require passengers to wear a mask during flights except for mealtimes, and some are blocking off middle seats to allow more distancing between people. Companies have also implemented rigorous cleaning procedures between flights. So how does this translate into overall risk?

"An airplane cabin is probably one of the most secure conditions you can be in," says Sebastian Hoehl of the Institute for Medical Virology at

COVID-19 Safety on Transportation

To assess your safety on an airplane, train, bus or shared automobile, look for how that form of transportation handles specific risk factors.

KEY:

Relatively safe | **Intermediate** | **Relatively unsafe**

Color coding indicates how safe each mode of transport tends to be in terms of each factor, compared with the others. The risk level of any individual trip depends on many factors and is virtually impossible to determine in advance.

Air filtration

- Most planes have HEPA filters, which capture more than 99 percent of airborne particles.
- Most trains use MERV filters. MERV-13 is recommended for viruses, but many subways have lower-rated filters.
- On buses, interior air is recirculated after passing through MERV filters akin to those found in a subway system.
- Most car air filters are designed for dust and particulates, not viruses.

Seat spacing/occupancy

- Some airlines have restricted occupancy of flights, but there is no guarantee of six-foot spacing.
- Some trains, such as Amtrak's, have been limiting capacity, but crowding may still occur.
- There are no occupancy restrictions on most buses.
- Uber and Lyft have restricted car-pool rides, but it is nearly impossible to maintain six-foot spacing in a standard car.

Time

- Flight times vary widely but virtually always exceed 15 minutes, the CDC's cutoff for "close contact."
- A subway ride can be as short as a few minutes. An intercity train trip might last hours.
- Long-distance bus rides tend to last for a greater amount of time than intracity commutes.
- Uber and Lyft rides tend to be relatively short, but trip times can vary widely.

Ventilation

- Planes have a mix of 50 percent outside air and 50 percent filtered air, with 20–30 air changes per hour.
- Trains replace air about 18 times per hour. Some trains also have windows that open, though this is rare.
- Some buses gain fresh air via ceiling vents, windows and door openings.
- Ride-share passengers can open windows, and the car's air circulation system can be set to take in outside air.

Mask policy

- Many airlines require masks, but this rule is not always enforced. Masks may be removed during meals.
- Amtrak and many subway systems require masks, but enforcement is not guaranteed.
- Most public bus systems require masks, but enforcement is not guaranteed.
- Uber and Lyft both require masks. Passengers may refuse a ride if the driver is unmasked.

Physical barriers

- Airplane bulkheads may serve as a partial barrier against larger droplets but likely won't block aerosols.
- Some trains have limited private rooms, but air circulation systems may be shared with the rest of the car.
- Some bus companies have installed plexiglass barriers around drivers but not between passengers.
- Some drivers have installed plastic shields that could block larger droplets but probably not aerosols.

AMANDA MONTAÑEZ

Goethe University Frankfurt in Germany, who has co-authored two papers on COVID-19 transmission on specific flights, which were published in *JAMA Network Open* and the *New England Journal of Medicine*, respectfully. Still, a handful of case studies have found that limited transmission can take place onboard. One such investigation of a 10-hour journey from London to Hanoi starting on March 1, 2020, found that 15 people were likely infected with COVID-19 in-flight—and that 12 of them had sat within a couple of rows of a single symptomatic passenger in business class. (The results were published recently in the U.S. Centers for Disease Control and Prevention's journal *Emerging Infectious Diseases*.) Most of these flights occurred early on in the pandemic, however, and in the case of the March 1 flight, masks were likely not worn, the researchers wrote. Meanwhile a recent Department of Defense study modeled the risk of in-flight infection using mannequins exhaling simulated virus particles and found that a person would have to be exposed to an infectious passenger for at least 54 hours to get an infectious dose. This finding assumes the infected passenger is wearing a surgical mask, however, and it does not account for the dangers involved in removing the mask for meals or talking or in moving about on the plane.

With flying, COVID risk really comes down to how closely one sits to other people and for how long, whether or not everyone is wearing a mask, and how infectious any passengers are at the time. If you happen to be seated close to a person who is actively "shedding" the virus, especially if it is a long flight or that person is not wearing a mask, there is a higher chance that you will get the disease. But if you are seated relatively far from others, and everyone is wearing a mask, your risk is probably fairly low. Being in a crowded airport or taking a taxi to get there could be a bigger concern, though.

"An airplane cabin is probably one of the most secure conditions you can be in."
—Sebastian Hoehl

Subways and Trains

Last spring the novel coronavirus tore through New York City, reaching a peak of thousands of new cases per day in April. Initially some researchers blamed the metropolis's bustling subway—which carried 5.5 million commuters on a typical pre-COVID weekday—for making it the epicenter of the pandemic in the U.S. But later reviews of the evidence suggest that mass transit systems have not been major drivers of viral spread. Last August the *New York Times* asked several international transportation agencies whether any superspreading events had been linked to mass transit, and they said that none had. A September report by the American Public Transportation Association (APTA) examined the coronavirus's spread in cities around the globe that had robust public transit systems. It found no correlation between mass transit use and transmission of the virus. Many of the cities in question required commuters to wear masks.

The APTA report suggested that commuters should reduce risk by wearing a mask and staying six feet apart and that train cars should be well ventilated. Most major cities' subways and trains constantly recirculate a mixture of fresh air and older air, both of which are pulled through a filter rated on the MERV (minimum efficiency reporting value) scale. MERV-13 filters are less efficient than HEPA filters, but the U.S. Environmental Protection Agency recommends them for reducing the number of airborne viral particles. A number of subway and train systems use lower-rated MERV filters that are still capable of at least reducing the volume of coronavirus in the air. The APTA report notes that on most systems' subway cars and buses, new air replaces stale air almost 18 times an hour. Passenger train operator Amtrak claims to cycle air through cabins 44 times an hour.

But even with fresh air available, an infected passenger can still transmit the coronavirus to someone who is sitting in close proximity—so riders should attempt to space themselves out and avoid densely packed cars whenever possible. Mask wearing reduces risk and is now mandatory on many forms of

transit in the U.S., including New York City's subway and bus systems, as well as Amtrak trains throughout the country. Finally, experts suggest that limiting the length of a ride can also be helpful: 15 minutes on a subway is safer than a multihour train trip.

Buses

Many buses have HVAC (heating, ventilating and air-conditioning) systems similar to those on subways and trains, with one additional factor: buses are more likely to have windows that open. Windows, as well as open ceiling vents, allow fresh air to enter the vehicle. In addition, in a city system (as opposed to a long-distance ride), buses make frequent stops. Doing so allows outside air to flood in each time the doors open. In a case study of a bus in China, a passenger with the novel coronavirus was able to infect many other riders, including those seated up to seven rows away. There seemed to be less risk of transmission, however, for people who were seated near windows and doors that could open.

In addition to snagging window seats, bus riders should look for the same safety features they would on a subway: a mask requirement, good ventilation and adequate spacing between passengers. Limiting rides to short trips may also be helpful. Some bus companies have installed clear partitions between drivers and passengers. Doing so might limit the spread of virus-carrying droplets from coughing, sneezing, breathing or speaking but is unlikely to prevent viral transmission via smaller airborne particles.

Taxis, Ubers and Lyfts

Before the pandemic, many people would not think twice about ordering a ride-share car or hailing a taxi. But now the idea of being in such an enclosed space with a stranger can seem like a life-and-death proposition. It is nearly impossible for drivers and passengers to remain six feet apart in a car, so transmission is definitely possible. An *NEJM* study in March reported on a Thai taxi driver who fell ill and tested positive for the coronavirus after driving some tourists who had been coughing but wearing a mask. Reliable data on the frequency of COVID transmission in cars is lacking, however.

Keeping the windows open and making sure the air system is set to take in outside air instead of recycling it should reduce the risk. Wearing a mask also probably helps, and ride-share companies Uber and Lyft both require drivers and passengers to do so. These companies have also stopped offering car pools (except in Uber's case for people who work together), so passengers are only exposed to the driver and anyone in their own party. Some drivers have even installed a plastic shield between the front and back seats. But as is the case with buses, these barriers would likely only protect against larger droplets, not aerosols. Shorter rides—especially those under roughly 15 minutes—pose a lower risk than long ones.

And keeping conversation to a minimum could also reduce the danger because talking is known to release aerosols that can spread the virus. If the rate of community transmission in your region is low, chances are that taking the occasional taxi or ride-share car is not a huge risk—provided you wear a mask and keep the windows open as much as possible.

—Sophie Bushwick, Tanya Lewis and Amanda Montañez

3-D Printing inside the Body Could Patch Stomach Ulcers

In vivo bioprinting might also help repair hernias and treat infertility

Stomach ulcers and other gastric wounds afflict one in eight people worldwide, but common conventional therapies have drawbacks. Now scientists aim to treat such problems by exploring a new frontier in 3-D printing: depositing living cells directly inside the human body.

Just as 3-D printers set down layers of material to create structures, bioprinters extrude living cells to produce tissues and organs. A long-term dream for this concept is that people on active waiting lists for organ donations—nearly 70,000 individuals in the U.S. alone, according to the nonprofit United Network for Organ Sharing—might one day have the option of getting a bioprinted organ. Although the ability to produce a functional heart or kidney this way likely lies years in the future, realistic near-term goals include

bioprinting simpler structures, such as bone grafts. Living tissues printed outside the body, however, would still require implantation surgery, which often involves large incisions that increase the risk of infection and lengthen recovery times.

What if doctors could instead print cells directly inside the body? The idea would be to use current minimally invasive surgical techniques to insert 3-D-printing tools into patients through small incisions and then lay down new tissues. Potential applications for such "in vivo bioprinting" might include surgical meshes to help repair hernias and patches for ovaries to help reverse infertility.

Much of the previous research on in vivo bioprinting has focused on treatments of skin and other tissues in the outer part of the body because the necessary equipment is normally too large to access the digestive tract and other centrally located organs without extensive surgery. In their effort to treat stomach lesions less invasively, scientists in China wanted to develop a miniature bioprinting robot that could enter the human body with relative ease. The researchers used existing techniques for creating dexterous electronic devices, such as mechanical bees and cockroach-inspired robots, says the study's senior author Tao Xu, a bioengineer at Tsinghua University in Beijing.

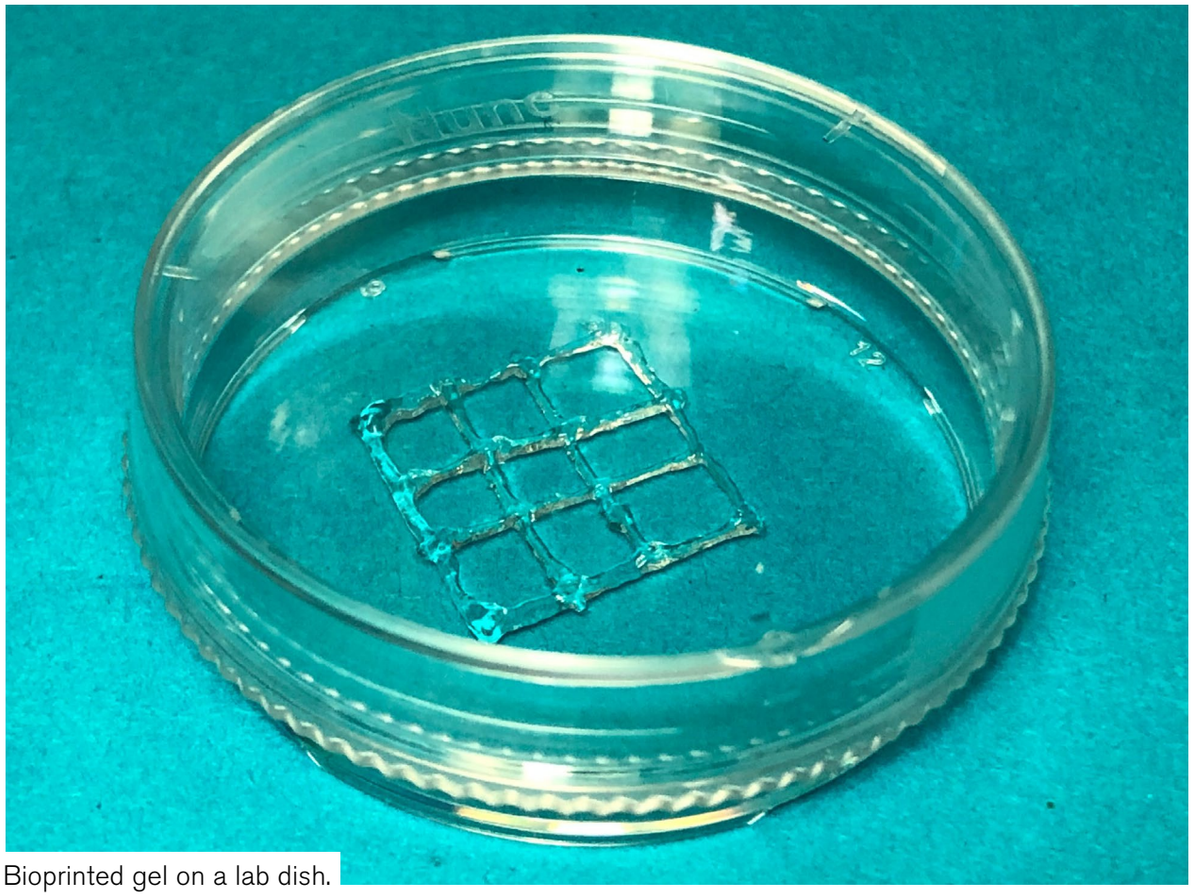
Bioprinting micro robot deposits live human cells onto a lab dish inside a transparent plastic model of a stomach.

The resulting micro robot is just 30 millimeters wide—less than half the width of a credit card—and can fold to a length of 43 millimeters. Once inside a patient's body, it unfolds to become 59 millimeters long and can start bioprinting. "The team has constructed clever mechanisms that make the system compact when entering the body yet unfurl to provide a large working area once past the tight constrictions at entry," says David Hoelzle, a mechanical engineer at the Ohio State University, who did not take part in the study.

In their experiments, the researchers in China fitted the micro robot onto an endoscope (a long tube that can be inserted through bodily openings) and successfully snaked it through a curved pipe into a transparent plastic model of a stomach. There they used it to print gels loaded with human stomach lining and stomach muscle cells (which were grown in culture by a commercial laboratory) onto a lab dish. The printed cells remained viable and steadily proliferated over the course of 10 days. "This study is the first attempt to combine micro robots and bioprinting together," Xu says.

The researchers say that mainstream gastric lesion treatments include medications, which can work slowly and are not always very effective; endoscopic surgery, which can only mend relatively small wounds; and endoscopically delivered sprays that staunch bleeding but are of little help in completely healing a larger injury. The hope for in vivo bioprinting is that it might eventually improve on these methods by patching over gastric lesions with living structures

WENXIANG ZHAO



Bioprinted gel on a lab dish.

that can repair them, Xu says.

Future research could bring the micro robot down to 12 millimeters wide and equip it with cameras and other sensors to help it perform more complex operations, Xu adds. He and lead study author Wenxiang Zhao of Tsinghua University detailed their findings last summer in *Biofabrication*.

Xu and his colleagues note that the gels they used as bioprinting "ink" were only stable when relatively cool. At normal body temperatures, they were too liquid to form structures well. Moreover the calcium chloride solution the researchers added to help solidify the gels could potentially damage the human body. But another gel, recently developed independently by Hoelzle and his colleagues, may help address these problems: it can hold its shape at body temperature and can be solidified using visible light.

One challenge with bioprinting is how to effectively attach printed cells to existing soft organs and tissues. Hoelzle and his colleagues tested a potential solution by trying to "heal" punctures in texturally similar materials—including raw chicken breast strips. First, the 3-D printer's nozzle extruded a tiny knob of bio-ink into the puncture, creating an anchor that could connect the pierced tissue to a bioprinted structure. Then they slowly withdrew the nozzle, trailing behind a strand of material they could use to lay more cells on the outside of the tissue. "This work is enlightening," Xu says. Drawing on these methods, he adds, will help the further development of in vivo bioprinting.

Hoelzle suggests that the technology will likely never become capable of printing complex organs. Instead it may prove useful by augmenting standard surgeries with relatively modest printed structures that could release drugs to promote healing or prevent infection. "There are many opportunities for tissue engineering materials … that are currently not considered—because no one would want to open up the patient to deliver the material," Hoelzle says.

—Charles Q. Choi

Dating during the Pandemic: Can You Trust an "Antibody-Positive" Claim?

Testing positive for COVID antibodies is not a pass to date freely

As many single people know, searching for love can be a challenge even in the best of times. But looking for it online during a global pandemic is something truly complex—and involves some tricky new dangers. Although some speculative swiping on dating apps has continued throughout quarantines and semi-lockdowns in the U.S., single people are reporting that in-person dating had basically frozen to a standstill until recent months. As cases surge again, many wonder whether it is safe to even consider meeting new people in any social context—let alone potential sexual partners.

Some online daters have adapted to the new normal and proudly declare on their profiles that they are "COVID-antibody-positive," apparently implying they have already had the virus and are now in the clear to

WENXIANG ZHAO

freely comingle. The COVID-19 pandemic is still solidly entrenched around the globe, with no widely available vaccine or cure. Does an antibody-positive test result translate to a pandemic dating hall pass?

"The data are clear that we don't know what is clear," says Peter Chin-Hong, an infectious disease specialist and a professor of medicine at the University of California, San Francisco. Even though antibody tests help to determine whether someone has previously been infected with the virus, that information may not be helpful in the dating realm. "There are a variety of tests, so just stating you're 'antibody-positive' doesn't provide evidence that equips someone to discern whether the test is [validated by the Food and Drug Administration] or specific to COVID. And we don't know how long antibodies from natural infections last. We're already starting to see reinfections emerge. Even if someone got a positive test result X time ago, that doesn't mean they're currently protected. It's not a passport to sexual freedom."

MALTE MUELLER *GETTY IMAGES*

A case study published in the *Lancet Infectious Disease Journal* last October described two instances of infection with SARS-CoV-2 (the novel coronavirus that causes COVID-19) in the same individual, a 25-year-old Nevada man who experienced more severe symptoms during his second bout. The authors concluded that "all individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2."

There have been at least four other confirmed reinfection cases, one each in Hong Kong, Belgium, the Netherlands and Ecuador. Researchers at Imperial College London recently found that the COVID-19 antibody response wanes over time. "It remains unclear what level of immunity antibodies provide," they concluded, "or for how long this immunity lasts." And of course, questions around antibodies apply to all social situations, not just online dating. That means upcoming holiday gatherings, weddings, parties and even just casual hangouts with friends are rife with uncertainty.

Dana (not her real name), a 38-year-old Tinder user in Portland, Ore., says she has encountered plenty of COVID-related content peppering the profiles of potential partners. "I've seen the occasional 'COVID-free' disclaimer in bios, which—like with STI status, how can anyone 100 percent trust [that]?" she says, referring to the practice of disclosing sexually transmitted infections (STIs) in dating profiles in the spirit of full transparency. But even though some parallels can be drawn between STIs and COVID (because both can have implications for partners' health), experts are quick to point out that the two categories are not equivalent.

"With HIV, for example, the antibody test is pretty durable, and we know what it means," Chin-Hong says. "People use it on the apps for

similar reasons, but it has a completely different meaning. With the COVID antibody test, people are intending to show that they're 'protected.' But that's not how antibodies work."

Antibodies are Y-shaped proteins that bind to viruses or other invaders in the body and trigger the immune system to destroy the harmful intruders. "Antibodies are the soldiers. I think of them as a viral stun gun that neutralizes a virus," Chin-Hong says. "You can get them artificially by having them infused. Or if you get the virus, you can develop them to protect you if you're exposed again." The issue, however, is that science does not yet know enough specifically about COVID-19 antibodies to be certain whether a positive test result actually indicates immunity.

Humans had never identified the novel coronavirus before this pandemic, and there are still plenty of unknowns surrounding the variability of its impact on our health. Some infected individuals produce high-quality antibodies that efficiently and accurately identify and eliminate the virus. Others produce weaker ones that afford partial protection. And some produce none at all. The current antibody tests do not account for that variability, making it impossible to know what level of immunity a person has (if any) or how long it may last.

"With HIV, for example, the antibody test is pretty durable, and we know what it means. People use it on the apps for similar reasons, but it has a completely different meaning. With the COVID antibody test, people are intending to show that they're 'protected.' But that's not how antibodies work."

—Peter Chin-Hong

According to physician James Zehnder, director of clinical pathology at Stanford Medicine, the inherent uncertainty of COVID-19 antibody testing makes it an unreliable method for screening dates. "Not everyone who has COVID has an antibody response," he says. "There are some false positive tests, and it's not clear for how long or how effectively these antibodies are protective." Zehnder says the best current test for excluding SARS-CoV-2 infection is a system called viral reverse transcription polymerase chain reaction (RT-PCR) , but even with that approach, false negatives are within the realm of possibility.

Charlie, a 37-year-old Grindr user in Brighton, England, who asked to be identified only by his first name, says that he deleted the app early on in the pandemic but has slowly started swiping again. "I had a couple of guys try to convince me that they'd already had COVID and have the antibodies, and [they were using] it like a hall pass for sex during the pandemic."

Dana says she has encountered straightforward dismissal of COVID-19 safety precautions. "The overwhelming direct message I get from guys is, essentially, 'The world is on fire. Let's throw caution to the wind and have sex as soon as possible,' " she says. "We're carnal beings. I don't deny that. But it's preposterous to me that in the middle of a global pandemic, some folks truly believe their handful of photos and a single sentence of noninfo is enticing enough for a girl to put her health at risk. Come on, gents, at least try and make us laugh first."

Chin-Hong says he understands the impulse to comment on antibody testing in the context of a dating profile. "Existentially, it says, 'I care about COVID, and I want to display that I took time out of my day to get tested and to show you that I'm willing to go the extra mile to engage with you,'" he says. "And it also says, 'I'm lonely, and I want to take things to the next level, and I'm done with FaceTime and being socially distant.'"

Camille (not her real name), a 30-year-old from California's Orange County, says she has encountered plenty of COVID-related remarks on the dating apps Hinge and Coffee Meets Bagel. When she matched with a hospital worker who expressed serious concern about the virus, she

felt an in-person meeting could be a reality. “We started chatting and then met a few times over video calls until we both felt comfortable meeting up for coffee safely and socially distanced,” she says. But then Camille’s would-be date contracted COVID-19. He was eager to reschedule, even before receiving a negative test result. “I was still uncomfortable and asked that we wait. He didn't take that very well,” she says. “He expressed that he didn’t have to share that he had COVID at all, which, to me, was terrifying—that there are probably people out there on dating apps, with COVID, not being considerate of who they’re meeting.”

After months of uncertainty, many people are still grappling with COVID-related questions, such as whether a person who currently has active antibodies can still transmit the virus to someone who does not. According to Chin-Hong, this is one scenario we may not need to obsess over. “It’s unlikely that an antibody-positive person will be able to efficiently transmit SARS-CoV-2 to an uninfected partner in general,” Chin-Hong says. “There is a theoretical risk that an antibody-positive person could act as a large surface—like a doorknob, you touch them and then touch your nose or mouth and theoretically get infected. But that’s unlikely, as it’s not the best transmission route.”

So what are singles to do in this atypical time? “My advice would be to take time to get to know someone before you meet in person,” says Melissa Cushing, director of transfusion medicine and vice chair of laboratory medicine at New York–Presbyterian Hospital and Weill Cornell Medicine. “Make sure you understand the COVID risks they take in their everyday life (not wearing a mask or avoiding large gatherings, et cetera) because their risks will become your risks. You should be comfortable with how they are handling COVID. A single laboratory test result will be much less important than everyday behaviors.”

In an attempt to alleviate some of the uncertainty-fueled pressure, apps are offering new digital dating options such as Bumble’s "virtual dating tools." And Tinder recently launched “Face to Face,” a new video chat feature. The app also consulted with Peter Pitts, president of the Center for Medicine in the Public Interest, to develop what Tinder calls “5 tips for getting back to IRL dating.” In addition to advocating mask wearing and social distancing during in-person meetups, Pitts encourages Tinder users to “get tested if you can but remember, even if you have antibodies, to always practice good health and hygiene. It is not yet clear that antibodies protect you or make you less of a carrier.”

Forty-year-old San Francisco resident Teresa (not her real name) has been using dating apps throughout the pandemic and says she is settling into the new normal of single life in the COVID era. “I’m going to keep dating,” she says. “I’m a responsible person, and I’m dating responsibly. You never know if someone is telling the truth anyway, so all you can do is take precautions and trust your gut.”

—Michelle Konstantinovsky

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These Drugs Might Prevent Severe COVID

Even with vaccines on the way, treatments are needed to prevent the disease from getting worse–and to be ready for COVID-25, COVID-37, and so on

By Charles Schmidt

ERNESTO BENAVIDES *GETTY IMAGES*

Charles Schmidt is a freelance journalist based in Portland, Me., covering health and the environment. He has written for *Scientific American* about therapeutic viruses that can infect harmful bacteria and about dangerous contaminants in drinking water.

IN THE YEAR SINCE THE COVID PANDEMIC BEGAN, GLIMMERS OF HOPE have come on the horizon. Vaccines are on the way, and the percentage of patients who die has fallen in many places as doctors have learned how to save the sickest patients.

These successes are not enough—and they overshadow the more limited progress made toward developing drugs that could prevent mild cases of the disease from worsening. Such treatments are urgently needed because many people will get sick with COVID until vaccines induce enough herd immunity in the population to keep the infections under control.

Antivirals and other drugs for early-stage illness could ideally prevent hospitalizations, shorten the duration of infectiousness and limit long-term complications from COVID. They may also prove useful against other threatening coronaviruses in the future. As of this writing, only two therapies for early COVID are available, and both of them come with major logistical challenges. But many other potential treatments are being developed that could save people from the worst outcomes.

Regeneron's monoclonal antibody combination for mild to moderate COVID, which was granted an emergency-use authorization by the Food and Drug Administration in November 2020, requires an hour-long intravenous infusion and another hour of monitoring for possible side effects. A second drug, the antiviral remdesivir, has shown promise in newly infected patients, but it requires five days of intravenous therapy. Demand for these medications, which were both administered to President Donald Trump and his allies during their illnesses, far outstrips current supplies. What doctors need are safe and effective treatments for early cases that they can give in outpatient settings "without overwhelming the health care system," says William Fischer, a pulmonologist at the University of North Carolina School of Medicine.

Drug development efforts aimed at treatments to contain the novel coronarvirus, or SARS-CoV-2, soon after infection are now ramping up. Physicians have a limited window of opportunity to hit the virus while it continues to replicate. Patients typically clear SARS-CoV-2 from their lungs and nasal passages within seven to 10 days, and after that, treatments aimed at curbing the pathogen become less effective. Even as viral loads plummet, immune reactions against SARS-CoV-2 can, in some patients, trigger out-of-control inflammation that destroys healthy lung tissue. At that point, treatment shifts toward drugs for severe COVID, such as dexamethasone, which ideally keep the inflammation in check.

In an interview with *Scientific American,* Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, described the desired characteristics of early COVID treatments. "My overwhelming preference is for direct-acting antiviral agents that can be administered orally" and that suppress the virus completely within a week or less, he said. "That, to me, is the highest priority."

Scientists have begun on differing paths to search for these drugs. By using machine-learning algorithms, they can quickly scour chemical databases for compounds with structural properties that might work against SARS-CoV-2. Promising candidates will then move from computer-modeling studies to research in human cell lines and experimental animals. Researchers are also using new protocols designed to shuttle drugs quickly from early- to late-stage clinical trials in outpatient settings. This approach "allows us to assess more compounds in a rapid, efficient way, although we are not rushing the scientific process for any of them," says Rachel Bender Ignacio, a physician-scientist at the Fred Hutchinson Cancer Research Center in Seattle.

Some of those drugs are repurposed medications that were initially developed for other diseases. Remdesivir, for instance, was targeted at Ebola and tested in human safety trials before being used later as a drug for COVID.

One of the current leading contenders for treating mild COVID is an antiviral pill that was previously developed for influenza. At first called EIDD-2801, the drug was found to protect mice from severe lung disease caused by two other coronaviruses—SARS-CoV and MERS-CoV. These results were from a study by research-

ers at the University of North Carolina at Chapel Hill (U.N.C.) and their colleagues that was published last April. Based on those findings, a Miami-based company, Ridgeback Biotherapeutics, licensed EIDD-2801, now called molnupiravir, for safety testing in people. Ridgeback has since partnered with Merck on a mid- to late-stage clinical trial, expected to wrap up within the year, to assess molnupiravir in nonhospitalized and hospitalized COVID patients.

Richard Plemper, a molecular virologist and biochemist at Georgia State University, has been working with the compound for years. He recently published a study showing that molnupiravir blocks SARS-CoV-2 transmission in ferrets, animals that scientists use to model human coronavirus exposures. "If the ferret data are indicative of what the drug can do in people, then it suggests we'll be able to therapeutically interrupt human transmission chains in people," he says. "And that would be a real game changer."

Repurposing existing drugs can also yield some surprises by finding ones that are not logical candidates to work against COVID-19. Fluvoxamine, a pill used for treating anxiety disorders, shows some promise in treating early COVID. Researchers at Washington University in St. Louis randomized 152 patients to fluvoxamine or a placebo and reported last November that none of the 80 patients who got the drug experienced worsening symptoms. In contrast, six patients in the placebo group became severely ill, and four were hospitalized.

Psychiatrist Angela Reiersen, a Washington University in St. Louis psychiatrist who conducted the study, explains that fluvoxamine acts on a protein called the sigma-1 receptor, which dampens the body's inflammatory responses to viral infection. She is now launching a larger trial across the U.S. and Canada. "We'd like to enroll people as soon as they have a positive test and some minor symptoms," Reiersen says. "The goal is treat before week two, which is when patients generally start to deteriorate."

"If the ferret data are indicative of what the drug can do in people, then it suggests we'll be able to therapeutically interrupt human transmission chains in people. And that would be a real game changer."
—Richard Plemper

Utilizing therapies that were initially developed for other purposes is not the only strategy. Drug designers have also come up with a computer-generated synthetic protein that disables SARS-CoV-2 before it gains a foothold in the body. At the University of Washington, researchers have devised from scratch proteins that bind to a spot on the virus's spikelike protrusions. These proteins—called mini binders—deflect the virus more effectively than antibodies in human cells, according to David Baker, a computational biologist who was senior author of the study. Baker says that in unpublished research, mini binders protected hamsters against SARS-CoV-2 infection. "We see this as a prophylactic nasal spray that you could use, say, if you're going to the airport or if you're a medical worker going into a risky situation," he says. Baker predicts that mini binders could enter human clinical trials against SARS-CoV-2 within six months.

In his interview with *Scientific American,* Fauci said that a single broad-spectrum drug that protects against many kinds of viruses is probably "a bridge too far." Yet what can be developed is a drug that works against multiple pathogens within the same viral family—perhaps one against multiple coronaviruses.

Virologist Ralph Baric and his team at U.N.C. have spent years working toward that goal. Much of the research is devoted to screening compounds against severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and SARS-like preepidemic bat coronaviruses in human cells and experimental animals. "When we started screening, we found some compounds that would only work against SARS and some that only worked against MERS," Baric says. "Then we found one that worked against both." That drug was remdesivir.

In follow-up research, Baric and his collaborator Timothy Sheahan of U.N.C. showed the drug could also inhibit SARS-CoV-2 in human lung cells and engineered mice. Yet remdesivir's Achilles' heel, Baric says, "has always been that it has to be given intravenously to people, which limits uses to hospitalized patients." In Baric's view, that explains the drug's inconsistent track record when it comes to speeding up COVID recovery rates: Doctors are often reluctant to admit people for treatment, he says, especially when beds are in short supply. By the time treatments begin, the virus is cleared, "and then it's too late," Baric adds. Remdesivir's manufacturer, Gilead Sciences, is now developing an inhalable form of the drug that should be easier to administer in outpatient settings.

Baric contends that evidence that remdesivir, molnupiravir and other compounds are able to block multiple coronaviruses suggests that broad-based antivirals are feasible. "Imagine putting a concerted effort into developing inhibitors for the viral families most likely to cause pandemic disease outbreaks around the globe," he says. "If we had those drugs on the shelf and ready to use immediately in an outbreak setting, we could save a ton of lives." SA

Psilocybin Treatment for Mental Health Gets Legal Framework

Oregon became the first state to legalize therapeutic use of the drug as new research affirms its benefits for treating depression

By Zoe Cormier

NICK VEASEY *GETTY IMAGES*

Zoe Cormier is a science writer based in London.

OREGON MADE HISTORY on November 3, 2020, becoming not just the first U.S. state to legalize psilocybin, the psychoactive compound in "magic mushrooms," but also the first jurisdiction in the world to lay out plans for regulating the drug's therapeutic use.

The next day, on the opposite coast, Johns Hopkins University researchers published results from the first randomized controlled trial of treating major depressive disorder with synthetic psilocybin. Their study, published in *JAMA Psychiatry*, found 71 percent of patients experienced a "clinically significant response" (an improvement that lasted at least four weeks after treatment). And 54 percent met the criteria for total "remission of depression."

At the U.S. federal level, psilocybin remains a completely prohibited Schedule 1 Drug, defined by the Drug Enforcement Administration as having "no currently accepted medical use and a high potential for abuse." But the state-level ballot measure and positive study results broaden the legal circumstances and settings in which the potent psychedelic can be used for mental health therapy.

"Our goal was to move psilocybin out of the medical framework so we could provide access to anyone who might safely benefit," meaning to allow its use by counseling therapists and not just by doctors in a hospital, says therapist Tom Eckert, co-author of the Oregon Psilocybin Therapy Ballot Measure, which passed with more than 1.2 million votes (55.7 percent). Although Oregon is not the first place in the U.S. to loosen restrictions on psilocybin—the cities of Oakland, Denver, Ann Arbor and Washington, D.C., voted in the past two years to effectively decriminalize the drug—it is the first to offer a framework for legal therapeutic use. "This is very different from decriminalization, which only seeks to lower the penalties for possession," Eckert notes. "We want to bring this therapy out from the underground and into [safe therapeutic environments]."

Such use will be tightly regulated, however: only licensed therapists and manufacturers will be allowed to grow the mushrooms or extract psilocybin from them or to synthetically produce the drug, set up a psilocybin therapy center or provide therapy. There will be no dispensaries selling mushrooms for recreational use, as exist for cannabis in California and 15 other states. People must be over 21 to receive the drug and may only consume it at a licensed facility with a certified therapist present. And Oregon will not be opening any legal psilocybin therapy centers until 2023 at the earliest, as the measure requires a two-year consultation with lawmakers.

The Oregon vote is the latest step in what many see as magic mushrooms' march to become "the next marijuana": a natural therapeutic and mood-altering compound gaining mainstream acceptance in a regulated market. Since 2015 psilocybin retreats have been allowed to operate in the Netherlands, where dozens of them cater to affluent tourists. Even there the drug exists in a legal gray area, however: psilocybin mushrooms are illegal, but "truffles" (clumps of the fungus's subterranean rootlike filaments) are legal.

PSYCHEDELIC MEDICINE

The potential benefits of psilocybin, LSD and other psychedelics were widely explored by psychiatrists in the 1950 and 1960s, before such drugs leaked from the lab and were embraced by the counterculture. A subsequent backlash led to a strict prohibition of legitimate research for the next four decades. But in recent years a handful of dogged psychiatrists have revived the field. A Johns Hopkins University 2006 double-blind study (meaning neither trial participants nor researchers knew if a subject was receiving psilocybin or placebo), published in the journal *Psychopharmacology,* demonstrated that psilocybin could give healthy volunteers "experiences having substantial and sustained personal meaning."

"What is different about psilocybin, compared to other mood-altering drugs or pharmaceuticals, is the enduring meaning and belief changes that can occur. People feel 'reorganized' in a way they don't with other drugs," says Johns Hopkins neuropharmacologist Roland Griffiths, lead author of the initial 2006 study as well as the latest one on depression. "It's almost like reprogramming the operating system of a computer." Griffiths now leads the new, $17-million-funded Center for Psychedelic and Consciousness Research at Johns Hopkins Medicine.

Dozens of other scientific reports in the past 15 years have built on the 2006 study, demonstrating psilocybin's

helpfulness for a variety of mental health conditions. In a 2016 paper in the *Journal of Psychopharmacology,* Griffiths and his team found that more than 80 percent of patients with a terminal cancer diagnosis experienced a "significant decrease in depressed mood and anxiety" after psilocybin combined with psychotherapy. In the same year, other researchers published the first study demonstrating psilocybin's potential to alleviate "treatment-resistant depression" that was not relieved by mainstream antidepressants. British researchers at Imperial College London described in *Lancet Psychiatry* the "marked and sustained improvements" in 12 patients suffering from this form of depression. This study, however, had no control (placebo) group. The latest randomized controlled trial from Johns Hopkins tested the drug in a double-blind study on 24 people suffering from major depressive disorder, which affects an estimated 300 million people worldwide. Roughly 20 percent of Americans will experience this form of depression at some point in their lives; by comparison, treatment-resistant depression is estimated to affect fewer than 5 percent.

In 2019 the U.S. Food and Drug Administration granted "breakthrough" status to a company called Compass Pathways to study the use of psilocybin—in conjunction with psychotherapy—for treatment-resistant depression. This means the FDA recognizes that the research "demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy" and that research and development will be "expedited."

"I welcome the broadening of the indications because I think psilocybin is likely to be effective in a range of disorders," says David Nutt, author of the initial 2016 study on psilocybin and depression and director of the neuropsychopharmacology unit in the division of brain sciences at Imperial College London. "However, it is critical that we have proper screening to protect people who might be vulnerable due to psychotic predispositions."

"We want to bring this therapy out from the underground and into [safe therapeutic environments]."
—Tom Eckert

Rachel Aidan, a professional therapist and CEO of Synthesis Group, a Netherlands psilocybin retreat center now looking to expand operations to Oregon, agrees. "As excited as we all are about the power of these compounds, the reality is that they are *not* for everyone," she says. "Right now we just need to keep our heads down to learn from the situation in Oregon and plan carefully for the future so we don't rush into legalization. We don't want to recreate the 1960s and the backlash that ensued."

AN ANTIDEPRESSANT ALTERNATIVE

Because psilocybin is thought to be most effective when given in combination with psychotherapy, the cost (possibly involving a dozen or more hours of therapy sessions) could remain in the thousands of dollars for the near future—and even more if the treatment involves synthetic psilocybin. Nevertheless, many hope the latest study will lead to psilocybin treatment being viewed more as a first line of defense for depression, rather than a quirky option for people who are desperate after conventional treatments fail. Psilocybin appeals to many because of the treatment's rapid and sustained effects, combined with the lack of unpleasant side effects such as weight gain and loss of libido, which are typically associated with widely prescribed SSRI antidepressants.

"This isn't about selling people a box of pills. This is about exploring a new way to deal with depression by going into the underlying issues," says Rosalind Watts, a psychologist who was formerly clinical lead on the psilocybin for depression study at Imperial College London. "It's not that this is better than antidepressants—it's just better for some people. Some people will still prefer antidepressants because they are simply more convenient. It just makes sense to have different options and for us to understand that different things work for different people at different times."

Watts has now left Imperial to operate as the clinical director at Synthesis, where she works to develop psilocybin therapies outside of medical academia. "Rather than conduct more small trials," she says, "I wanted to help set up something for people to access psilocybin therapy now."

Actions like this by clinicians around the world are nudging psilocybin from a fringe treatment toward mainstream medicine. As Rick Doblin, founder and executive director of the Santa Cruz, Calif.–based Multidisciplinary Association for Psychedelic Studies, puts it: "Our long-term goal is mass mental health."

Johns Hopkins and Imperial researchers have already planned more psilocybin studies for a range of difficult-to-treat conditions, hoping to harness the drug's ability to "unblock" people by shifting perspectives, catalyzing insights and changing problematic and habitual mindsets and behaviors. Studies on anorexia, obsessive-compulsive disorder, smoking cessation, opiate addiction and post-traumatic stress disorder are all in the works.

Griffiths, however, is wary of efforts to rush the drug out from tightly regulated settings. "I'm sympathetic to people who are impatient, but we don't want to end up in a situation where people underestimate the potential risks of using these compounds. They do have significant risks, such as panic, anxiety and dangerous behavior," he says. "In Oregon, the devil is in the details in how things will unfold." SA

Despite signs of reduced influenza transmission, people in the U.S. are being encouraged to get the vaccine.

JEFFREY GREENBERG *GETTY IMAGES*

How COVID-19 Is Changing the Cold and Flu Season

Measures meant to tame the coronavirus pandemic are quashing influenza and most other respiratory diseases, which could have wide-ranging implications

By Nicola Jones

Nicola Jones is a freelance writer based in Vancouver, B.C.

BY MID-DECEMBER THE NORTHERN HEMISPHERE IS USUALLY WELL into the start of its annual cold and flu season—but in 2020, even as the COVID-19 pandemic surged in dozens of countries, the levels of many common seasonal infections remained extremely low.

By January 2021 the pandemic caused by the SARS-CoV-2 coronavirus had infected nearly 83 million people and killed almost 1.8 million worldwide. The patchwork of responses intended to fight the pandemic—from temporary lockdowns to mask wearing, social distancing, enhanced personal hygiene and reduced travel—has had a huge impact on other common respiratory illnesses, too.

In the Southern Hemisphere—now past its winter—seasonal influenza hardly struck at all. That looks as though it might happen in the north, too. Conversely, some common-cold viruses have thrived, and tantalizing evidence suggests that they might, in some cases, protect against COVID-19.

Despite humanity's long history with colds and flu, the viruses that cause them still hold many mysteries. Scientists hope this year's disrupted seasons could reveal new information about the transmission and behavior of these unwelcome annual guests: how these viruses respond to health measures, how they interact and what that might mean for long-term disease burdens. "This is a natural experiment for so many respiratory viruses," says Sonja Olsen, an epidemiologist at the National Center for Immunization and Respiratory Diseases, part of the U.S. Centers for Disease Control and Prevention.

THE INFLUENZA FIZZLE

Last May, at the tail end of the first wave of COVID-19 deaths in many nations, and when some of the strictest lockdowns were in place, health workers noted an abrupt and early halt to the 2019–2020 flu season in the Northern Hemisphere.

That might partly have been an artifact caused by fewer people coming to a clinic for testing, experts say, but it was also attributable to the effectiveness of policies such as social distancing. After the pandemic started, positive tests for the flu virus plummeted by 98 percent in the U.S., for example, whereas the number of samples submitted for testing dropped by only 61 percent. In the end, the U.S. 2019–2020 flu season was rated as moderate by the CDC, which estimates that 38 million people fell ill with influenza, and 22,000 people died. That is fewer than in recent years but not unprecedented.

After the flu season in the north ended early, it hardly got going at all in the Southern Hemisphere. There were astonishingly few cases of seasonal flu there from April to July 2020—even as global COVID-19 cases continued to climb. In Australia, Chile and South Africa, a grand total of just 51 cases of flu were spotted in more than 83,000 tests. "We know it's less transmissible than coronavirus, so it makes sense," Olsen says, but the decline was still "greater than expected." Influenza's absence has been attributed to pandemic-response measures, but they don't tell the whole story.

"Some South American countries haven't done such a good job controlling COVID, but even there flu is low," says virologist Richard Webby of St. Jude's Hospital in Memphis, Tenn. "I don't think we can put it all down to mask wearing and social distancing." He suspects that the dearth of international travel played a part. Flu typically travels around the world from one winter to another, while maintaining a lower year-round presence in the tropics. Although the mechanisms underlying this behavior aren't entirely clear, the movement of people clearly contributes.

Increased influenza vaccination might have contributed to the disappearance, too. Australia, for example, saw more than 7.3 million flu jabs administered by May 20, 2020, compared with 4.5 million by that date in 2019 and 3.5 million in 2018. It's unclear if that trend will hold in the north.

Vaccination rates in the U.S. for seasonal flu have been trending upward for years: slightly more than half of the U.S. population over six months of age was vaccinated in

2019–2020, up 2.6 percentage points from the previous year. But it is unclear whether Americans will be more or less inclined toward flu vaccinations this year, particularly given the tumultuous backdrop of the pandemic and the change in president.

VIRAL UNKNOWNS

Most experts are cautiously betting on a very mild flu season for the Northern Hemisphere this year. That would be good news on many fronts—in particular, it would help to alleviate the potential burden on the health system, from hospitals to testing centers, caused by simultaneous waves of flu and COVID-19. But surprises could be in store.

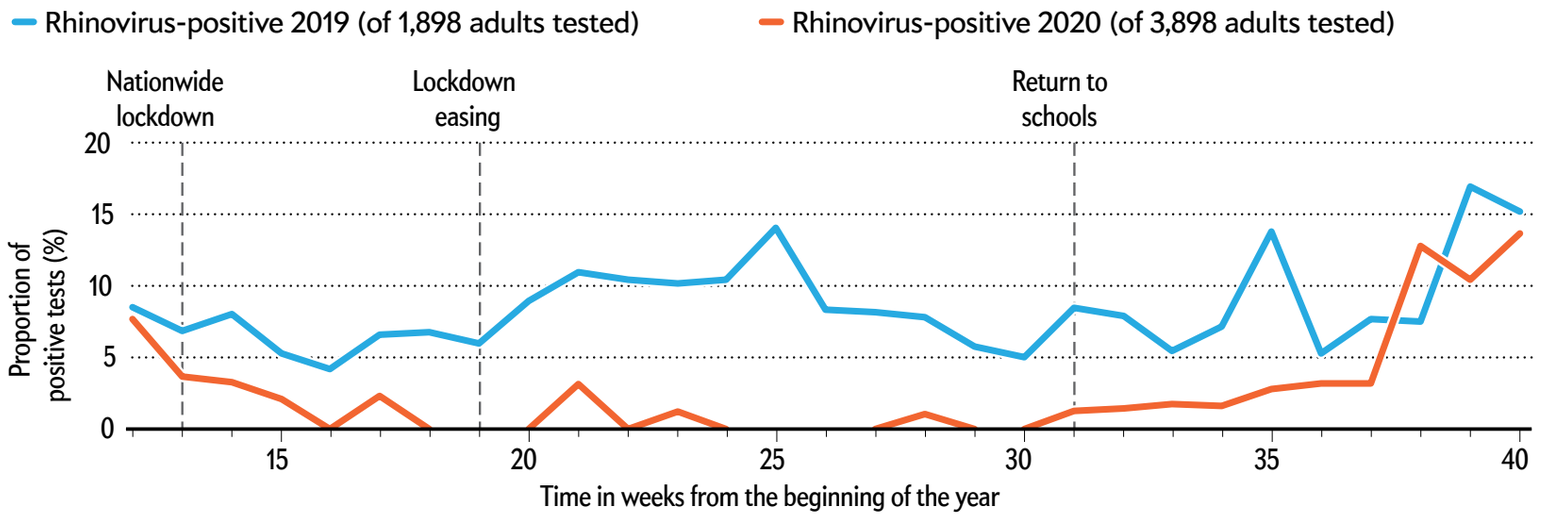
No one really knows, for example, why one nation, such as Australia, can be hit hard by influenza for several years while a neighboring country, such as New Zealand, sees very low rates, Webby says. Even influenza's seasonality isn't entirely understood, nor exactly how it travels around the globe. "We don't have a real good handle on why it's a winter disease," he says. Untangling lessons about flu from this year's data will be interesting but difficult, Olsen says, because pandemic policies and compliance vary on the national, state and even neighborhood level.

And the changing trends could have consequences. If this year's flu season does fizzle out in the Northern Hemisphere, that could make it harder to predict the right strains to put in 2021's flu vaccine. It could also have intriguing, longer-term consequences. Webby speculates that a low-flu season might kill off less common variants of influenza. "A lot of different flus have been circulating in recent years. Are they all going to make it out of this or not?" he asks. "It's possible that what this season will do is actually make the virological picture a lot simpler. That may be permanent, potentially."

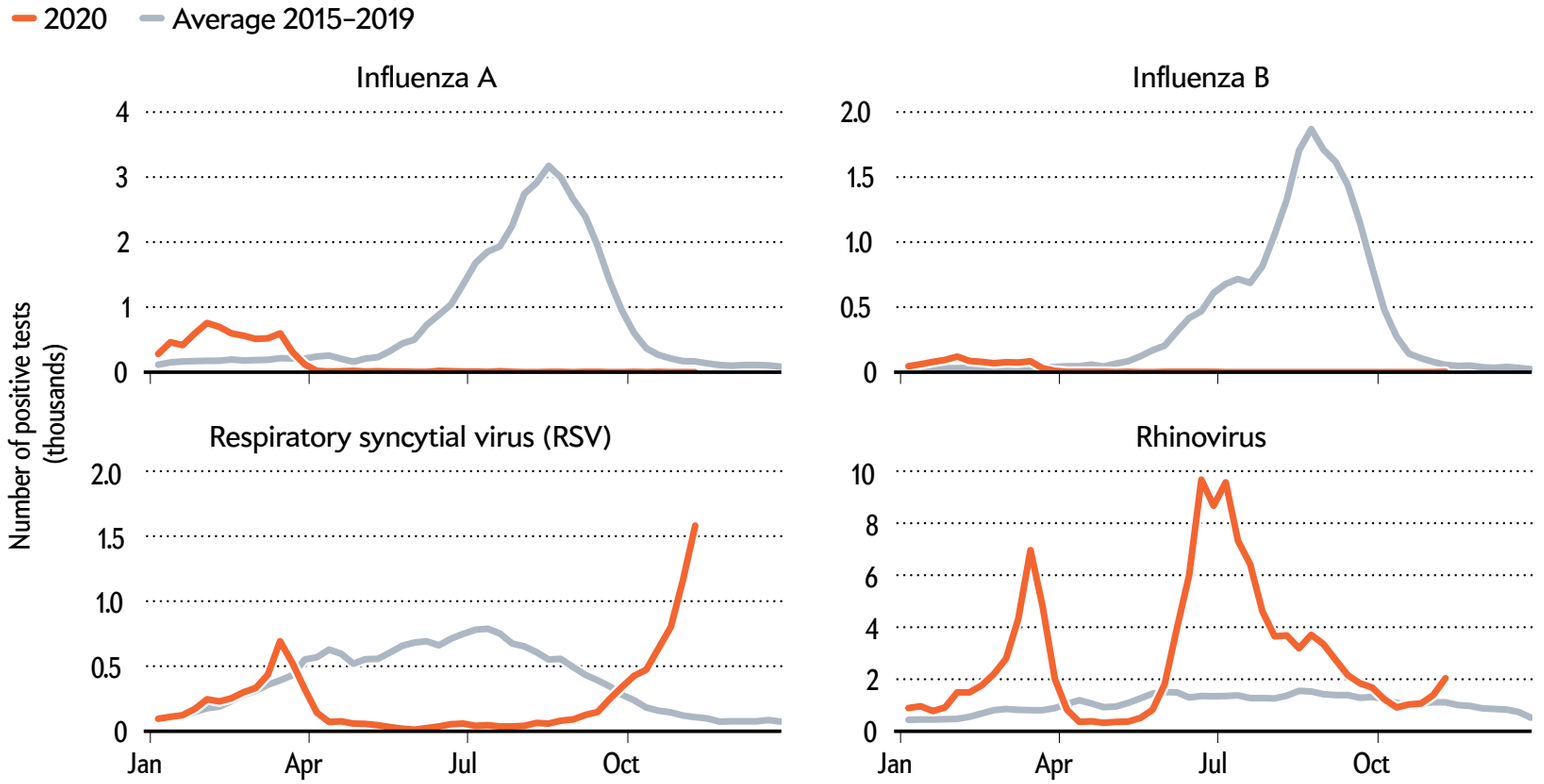
At the same time, Webby adds, the lack of viral competition in human hosts could conceivably open a door for new swine-flu variants in the future. "We get a handful of

Shifting Patterns of Colds and Flu

Following the United Kingdom's national lockdown in March 2020, there was a drop in detection of most common respiratory viruses, including rhinovirus. Infections didn't rise when lockdown eased, but they did rise rapidly after schools started again in September.



Data from New South Wales in Australia show large declines in influenza detection this year relative to previous ones. Respiratory syncytial virus (RSV) also decreased to lower levels than usual but bounced back rapidly in October. There were large spikes of rhinovirus detection, however, compared with previous years, although this might have been due to increased testing.



SOURCES: UK: REF. 4; NSW: NSW MINISTRY OF HEALTH

those every year, in the agricultural-fair season," Webby says. "One of the things holding those viruses back a lot is natural immunity. If flu is low for a few seasons, that might leave a gap for swine viruses to have more impact."

"I am sure that flu will come back with a vengeance at some stage in the future," says Robert Ware, a clinical epidemiologist at Griffith University in Queensland, Australia, "but it might take a few years."

BUCKING THE TREND

Influenza viruses aren't the only ones affected by pandemic-response measures. There are hundreds of viruses that cause respiratory symptoms similar to those of a common cold, from parainfluenza to metapneumovirus. And most of these viruses, too, seem to have been held at bay in the Southern Hemisphere's winter.

In particular, researchers saw some abrupt declines in respiratory syncytial virus (RSV), a common virus that typically infects young children and can sometimes cause serious conditions such as pneumonia. There is no vaccine for RSV, and the virus causes about 5 percent of deaths in children under five around the world. In Western Australia, RSV in children declined by 98 percent (and flu by 99.4 percent) through their winter 2020, even though schools were open.

Enhanced school cleaning might have reduced the spread of some viruses, but others persist.

OLI SCARFF *GETTY IMAGES*

The RSV reprieve might be only temporary, though. Data from Australia's most populous region, New South Wales, for example, show RSV detections climbing back up in October. And a build-up of susceptible, uninfected children might result in bigger waves of infection in future, some researchers warn.

There is one major exception to the downward viral trend. "The one virus that's not being halted is the rhinovirus," says Janet Englund, a pediatric infectious disease researcher at Seattle Children's Hospital. Rhinoviruses are the major cause of the common cold, especially in children. More than 100 strains exist, and about a dozen typically circulate in any given community. In one study in Southampton, England, rhinovirus detection in adults admitted to hospital remained lower over the summer of 2020 than in the summer of 2019 but shot up as usual once schools reopened in September. Data from NSW likewise show an apparent surge in rhinoviruses over the southern winter. Although some of these peaks are probably the result of an increase in testing in people with mild cold symptoms, these viruses certainly did not decline as others did.

"No one really knows why" rhinoviruses are proving so persistent, Englund says. Some viruses that cause coldlike symptoms are very different from one another in structure; in particular, rhinoviruses, unlike influenza and coronaviruses, don't have an outer lipid coat, or envelope, which is vulnerable to soaps and sanitizers. In NSW, detection of the nonenveloped adenoviruses, which also cause coldlike symptoms, held relatively steady throughout the southern winter, rather than crashing like flu or surging like rhinovirus. "The expectation is that rhinovirus is perhaps more stable on surfaces," Englund says, allowing greater transmission between children on hands, desks and doorknobs. There is also thought to be greater asymptomatic transmission of rhinoviruses,

which would allow them to circulate more freely in schools, even when sick children are staying at home.

The good news is that the common cold might help to protect people against COVID-19. One study of more than 800,000 people, for example, showed that adults who had had cold symptoms within the previous year were less likely to test positive for SARS-CoV-2—although why this is so remains a mystery.

CROSS-PROTECTION?

One possible explanation is that previous infection with a coronavirus (another cause of the common cold) could confer some immunity to SARS-CoV-2—although it is notable that people can get the same coronavirus colds over and over again and multiple cold viruses at once. Previous coronavirus infections do seem to generate T cells and B cells—immune system cells that help to attack and remember pathogens—that can recognize SARS-CoV-2. These preexisting cells might provide some partial cross-protection against the new coronavirus.

A few studies have shown that because of other coronavirus infections, about one quarter of people have antibodies that can bind to the SARS-CoV-2 virus, says Scott Hensley, a viral immunologist at the University of Pennsylvania. One study showed that these antibodies can actually neutralize SARS-CoV-2 infections, stopping the virus from invading cells. Strong cross-neutralization of SARS-CoV-2 by antibodies against other coronaviruses would be "really spectacular," says Qiuwei Abdullah Pan of Erasmus University Medical Center in Rotterdam, the Netherlands, because it would open the door to universal coronavirus vaccines that protect across the board. But other studies, including Hensley's, found that these antibodies cannot neutralize SARS-CoV-2 or protect against COVID-19. "Cross-neutralization has not been proven," Pan says. Even if it is, he adds, "I would expect the activity would probably be very moderate."

Another way that seasonal colds might be contributing to COVID-19 immunity is that a current rhinovirus infection might interfere directly with SARS-CoV-2—perhaps by kicking off interferon responses, part of the immune system that inhibits viral reproduction. A study by Ware and his colleagues, for example, shows that someone with a rhinovirus infection is 70 percent less likely to also get a common coronavirus infection, compared with someone who doesn't have the sniffles. Clinical microbiologist Alberto Paniz Mondolfi of the Icahn School of Medicine at Mount Sinai and his colleagues have shown markedly few rhinovirus co-infections in people with SARS-CoV-2 in New York City. "Rhinovirus is one tough virus," Paniz Mondolfi says. Its fast growth stops other viruses from taking off, and it could conceivably be outcompeting SARS-CoV-2, he says.

This viral interference might be a powerful effect. Ellen Foxman, an immunologist at the Yale School of Medicine, and her colleagues have found evidence that rhinoviruses might have derailed the influenza H1N1 pandemic that occurred in 2009, for example. Hospitalized adults had fewer than expected instances of co-infection with both viruses. And in cell cultures, rhinovirus infection stopped that strain of H1N1 from infecting cells. Foxman is now looking to see whether rhinovirus infection can block SARS-CoV-2; she expects results soon.

Overall, it's a "very likely scenario" that rhinoviruses and other coronaviruses will help to stem the spread of COVID-19, Paniz Mondolfi says. "I think many virologists, like me, have been waiting for this season to look at how this will evolve."

But with so many unknowns surrounding all these viruses, most researchers say that people should be ready for a worst-case scenario—from a bad flu season compounding the challenges of COVID-19 to future outbreaks of RSV. "It's best to be prepared," Olsen says. "We don't know what's going to happen." SA

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BEHAVIOR & SOCIETY

Abortion and Contraception in the Middle Ages

Both were far more common than you might think

Today conversations around abortion in modern Christianity tend to take as a given the longstanding moral, religious and legal prohibition of the practice. Stereotypes of medical knowledge in the ancient and medieval worlds sustain the misguided notion that abortive and contraceptive pharmaceuticals and surgeries could not have existed in the premodern past.

This could not be further from the truth.

While official legal and religious opinions condemned the practice, often citing the health of women, a wealth of medical treatises produced by and for wealthy Christian women across the Middle Ages betray a radically different history—one in which women had a host of pharmaceutical contraceptives, various practices for inducing miscarriages, and surgical procedures for the termination of pregnancies. When it came to saving a woman's life, Christian physicians unhesitatingly recommended these procedures.

Since antiquity, the termination of pregnancies has long been associated with women at the margins of society, such as sex workers, and highlighted not only for the termination of the fetus's life but for the great danger it posed to women. For instance, in the Hippocratic Oath, Hippocrates refuses to assist in or recommend euthanasia and additionally refuses to give women abortifacients given the danger in which they put the life of the mother.

Illustration from *De materia medica,* a sixth-century manuscript about medicinal herbs.

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Religiously, the Church Council of Ancyra in 314 A.D. stated that women found to have committed or attempted an abortion on themselves or others were to be exiled from the Church for 10 years, revising earlier suggestions that they be exiled for life. Yet in the mid-fourth century, the Church Father Basil the Great revises these decrees, suggesting that time should not be proscriptive but dependent on the repentance of the person. There, however, he focuses not just on the fetus but again on the danger of these procedures for women, who "usually die from such attempts."

The laws of the early Christian world generally reflected these prohibitions, outlining exile as the punishment for whoever has undertaken an abortion or aided in one—or death if the person dies in the process. Many of these laws were codified in the sixth-century *Digest* of Justinian, a legal compendium culled from ancient legislative opinions.

Nevertheless, these legal opinions betray the real complexity that abortions had in the ancient and medieval worlds. For example, the *Digest* cites the opinion of the jurist Tryphonius, where a woman was sentenced to death for undertaking an abortion, precisely because she did so with the malicious intent of denying her husband an heir by aborting the unborn inheritor. Legally, we see abortions being intimately associated with a patriarchal control of lineage and reproduction. The *Digest* clarifies that if a woman undertakes an abortion after a divorce, "so as to avoid giving a son to her husband who is now hateful," however, she should only be temporarily exiled.

The fourth-century Church Father John Chrysostom even turned these stereotypes on their head. Though criticizing abortions, in one sermon he offers the example of a sex worker forced to have an abortion so as to not lose her livelihood. While damning the act as a murderous practice, he places blame not on the woman but on her client, chastising the man by saying that the sex worker cannot be criticized for seeking out an abortion, writing that while "the shameless act is hers, the cause of it is yours." Thus, it is the sex worker's client who is the cause of the murder, not she who requires her attractive body to survive.

Despite the prohibition in the Hippocratic Oath, gynecological texts were replete with recipes for contraceptive and abortive suppositories. The second-century gynecology of Soranus of Ephesus details these recipes and advocates their use for women who have a medical reason to prevent pregnancy, strongly opposing their use simply "because of adultery or out of a consideration for youthful beauty," given the health risks involved. Thus, adultery and a conceited desire to preserve one's good looks were often lodged against women known to practice abortions.

The recipes of Soranus were transmitted across the centuries in various texts, each demonstrating an active history of use and commentary. For example, in Aëtius of Amida's sixth-century medical treatise, the author details the use of contraceptive vaginal suppositories, elaborating on the improvements to the recipe from Soranus's time. There Aëtius writes that once the contraceptive has been used, "if she wishes, [the woman] may have intercourse with a man. It is infallible because of its many trials."

Aëtius's gynecological treatise has often been associated with the patronage of the elite imperial circle of Empress Theodora in Constantinople, an empress whom the court historian Procopius once described as often conceiving, "but by using almost all known techniques she could induce immediate miscarriage." The use and efficacy of contraceptives and abortifacients extend throughout the Christian Middle Ages. In one 12th-century text from Salerno, the author offers the example of sex workers, who frequently have intercourse yet only rarely conceive.

Therefore, the medical historical evidence proposes a very different story from that told by official religious or legal texts. The fact of the matter is that good Christian women were indeed undertaking abortions and using contraceptives. Yet wealthy and elite Christian women had not only recourse to the best medical knowledge of their era but also the privacy to undertake these practices without shame.

Most surprisingly, however, these medical practices were not only relegated to herbal, pharmaceutical contraceptives and abortifacient drugs but also the various surgical interventions, what today we would refer to as a late-term abortion.

In the early 10th-century *Life of Patriarch Ignatios,* by Nicetas David Paphlagon, a narrative of a religious figure, the author recounts the story of a woman in labor with a breeched birth. There

she is in immense pain, and the author writes that "in order to prevent the woman too from perishing with her child, the doctors [attended] to operate on the baby and draw it out by cutting it limb by limb." While the procedure ultimately does not need to happen thanks to the miraculous workings of a relic, the author, without any moralization or shame, details here the contemporaneous procedures for an embryotomy, as described in medieval surgical manuals.

Further corroborating the continued use of this surgery, we can note that the sixth-century text by Aëtius of Amida (citing a certain Philumenos and Soranus) details the operation for an embryotomy similarly. The same operation is also recounted perfectly in Paul of Aegina's own seventh-century compendium on surgical practices.

These late-term abortions echo their modern counterpart, demonstrating that this was a known and established practice in the Middle Ages. This medical knowledge flourished in particular in the Greek-speaking, eastern Roman Empire, most commonly known to us today as the Byzantine Empire. Glimmers of the medical prowess of the Byzantine Empire and its long-thriving history are scattered across medieval sources.

In fact, one of the first recorded uses of a cesarean section on a living woman comes down to us from Visigothic Spain, but the text tells us the deed was performed by a skilled "Greek" (aka Byzantine) doctor, who is called to save the life of a living mother whose child has died in the womb.

While cesareans were used in antiquity, they were deployed then only to rescue a child from a dead mother. In the *Lives of the Fathers of Mérida,* composed in the 630s, the author chronicles the life of Paul, bishop of Mérida around 540–550. Paul is a Greek who had trained as a doctor in his youth. To save the life of a wealthy woman, he must put his clerical garments aside and sully his hands with an embryotomy. The text describes how "with wonderous skill he made a most skillful incision by his cunning use of a knife and extracted the already decaying body of the infant, limb by limb, piece by piece," in order to save the woman's life.

The only difference between the figure of the sex worker shamed for her abortions and the persons for whom these gynecological and surgical books were commissioned is that the latter were courtly elites. Therefore, they had better recourses to medical knowledge, treatment and privacy.

But the fact that stories of late-term abortions even find their way into saints' lives without judgment belie a more important fact: that abortions undertaken for the preservation of a woman's life or health were rarely, if ever, under attack by medieval Christian authors. Not even the moralizing religious texts touch on such cases. This is a fact that modern Christian pundits have not merely forgotten but just never learned.

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MEDICINE

Your Tears Might Save Your Life Someday

They could ultimately be used to find diseases the way blood tests do now—but cheaper and more easily

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At any given moment, about seven microliters of tears are present in each of our eyes—about a tenth of a drop of water. You might think of them as nothing more than salty water, but it's more accurate to think of them as filtered blood; they deliver oxygen and nutrients to our eyes, removing waste, serving as the first line of defense against pathogens and helping to heal injuries.

Tears also contain traces of the various chemicals originally present in blood, some of which serve as markers of illness—glucose, for example, which can signal diabetes, or enzymes that point to possible liver disease. That's a primary reason doctors order blood tests. But it also that means that physicians—and maybe, in the near future, you—can look for indicators of illness by looking at your tears.

Research has already shown that markers of many of the most common and devastating diseases, such as cancer, multiple sclerosis, diabetes mellitus, cystic fibrosis and Parkinson's, are found in tears. Work is already underway to validate the use of such markers for diagnosing Alzheimer's disease. And recently a technology named TearExo has been developed for breast cancer screening using tears collected by patients themselves. That could greatly reduce

the costs of testing and allow earlier detection of malignancy than mammograms can provide.

Tear testing could also make an impact in the COVID-19 pandemic: current research has focused on developing a test to diagnose SARS-CoV-2 infections, as well as document prior infections, through antibody testing. These assays are typically done with blood—but coronavirus RNA has been detected in tears as well, and antibodies to the virus may also be measured from tears. That means a rapid and cheap tear test could be developed in the near future—and because no needles are involved, this, too, could in principle be self-administered at home.

But the potential advantages of tears as indicators of health go beyond occasional testing. One promising tear-based technology is a smart contact lens that continuously monitors a patient's biomarkers, significantly improving disease prevention and early detection; it has attracted the attention of Novartis and Google, among other major companies, and is currently under development in research laboratories around the world. One significant step in its development was the first stand-alone contact lens with an integrated battery in 2019. More recently, a smart contact lens has been successfully developed for continuous glucose monitoring and treatment of diabetic retinopathy. Such a product probably won't be ready for commercial use for several years. But according to the Centers for Disease Control and Prevention, about 45 million people in the U.S. already wear contact lenses to correct their vision. Switching to a smart version would be simple for them—and of course, you can wear smart lenses even if your vision is perfect,

As with detecting diseases, we can use mouse models to find tear markers for conditions ranging from environmental pollution to chronic stress to drug abuse. In 2019 I worked on developing a technique allowing the first-ever metabolite marker screening from mouse tears. This was a challenge because a mouse's tears have less than 10 percent of the volume of human tears. I was able to overcome this challenge by using thin threads to absorb very small amounts of liquid from the surface of the eye, similar to how a paper towel absorbs water.

Interestingly, in 2018, NASA proposed to use tear markers to monitor astronauts' health in space. This would allow us to better understand the effects on human health of long-term exposure to space environmental factors such as radiation and weightlessness. Tear markers from veteran astronauts and new astronauts without space exposure would be used to establish a health database, which might be one of the first stepping-stones toward making space colonization a living reality.

This is just the tip of the iceberg when it comes to the potential in tears beyond crying. Tears can provide an inexpensive, rapid and easy-to-use alternative to monitor health. Given the unprecedented advantage in tear technology to externally and continuously monitor health and to be used even by the healthy, such technology will almost certainly lead to more effective prevention of diseases—rather than having to deal with the difficulties of treating them.

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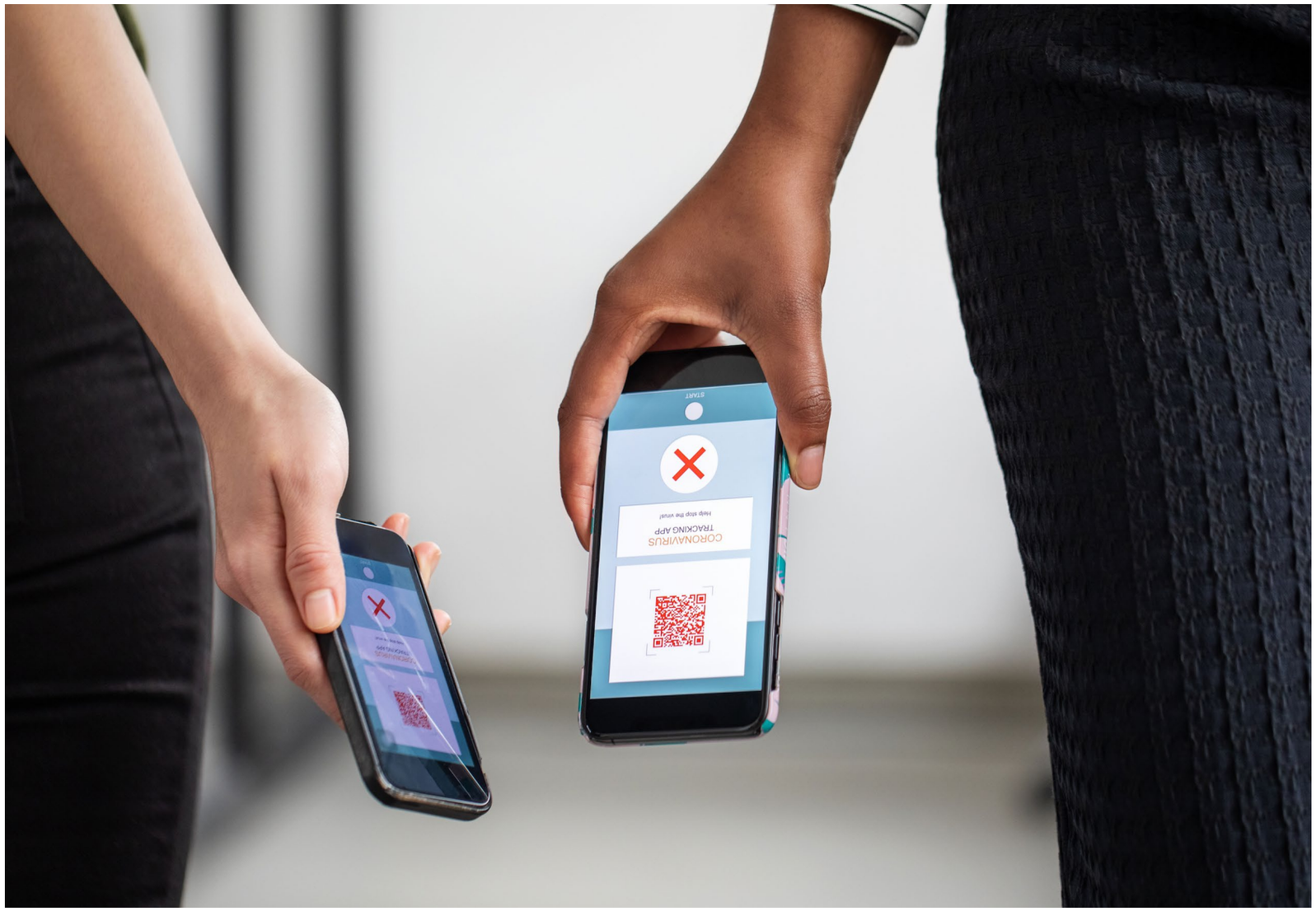
PUBLIC HEALTH

How to Fix COVID Contact Tracing

Apps and human tracers both have pros and cons. To be effective, they have to work together



LUIS ALVAREZ *GETTY IMAGES*

As coronavirus cases reach new peaks, surpassing 200,000 cases a day in the U.S., public health departments are overwhelmed. Departments are racing to hire yet more contact tracers, and some are even asking people to do their own contact tracing and notification. Other states are just now pushing out big tech's solution to the pandemic: mobile contact tracing apps.

Initially the hope was that contact tracing apps would be a silver bullet for contact tracing. Evidence shows this is not the case. Many European countries have been using these apps for months with limited success.

As a result, some public health departments are taking matters into their own hands, turning away from big tech and innovating their own technology solutions. Early evidence suggests these solutions may work better both for public health and for the public.

Traditional contact tracing works by interviewing those infected with COVID-19 about whom they have encountered during the prior two weeks. The contact tracers then contact those who have been exposed to notify them of exposure. But the relationship does not end there.

Contact tracers ask those who have been exposed to monitor their symptoms, for example, by taking their temperature twice per day. They call back frequently to collect symptom data and ensure that those who become ill get appropriate care and avoid infecting others. Contact tracers

seek to build trust with those they are in contact with, to encourage truthful and accurate reporting from those they contact.

Before the pandemic hit, the U.S. employed about 2,200 contact tracers. The American Medical Association estimates that more than 100,000 contact tracers are needed to address the pandemic.

Contact tracing apps aim to fill this gap by automating the contact tracing process. The apps track when app users encounter one another. If a user later uploads a positive coronavirus test result, app users who've been exposed can be notified, all through the app.

But contact tracing apps have struggled with low adoption rates, issues with the accuracy of the Bluetooth technology on which the apps rely to detect when app users come into contact with one another, and ensuring that app users remember to bring their phones with them and to upload their coronavirus test results.

These struggles have arisen, in part, because of how and why contact tracing apps were created. Contact tracing apps were imagined and developed by technology companies with little input from public health experts or the public the apps are designed to serve.

When tech companies impose technologies in domains they do not understand, they often fail. Consider the massive open online courses that technologists once dreamed would replace traditional degree programs or Google Health, intended to solve the issue of medical records sharing from the patient perspective.

Faced with this new surge, some public health departments have started building their own solutions. They are leveraging their experience with contact tracing and the technology they already have in order to scale contact tracing efforts.

For example, in Michigan, Ottawa County's public health department automated contact tracing symptom checks and follow-ups by repurposing their existing OnBase case management software and online survey tools

Ottawa contact tracers make first contact with at-risk individuals the traditional way: with a phone call from a trained contact tracer who can collect the necessary information and establish a relationship.

Follow-ups for symptoms, however, are done by sending a simple two-question survey via text message to those who have been exposed and added to the contact tracing database. Public health data analysts can analyze symptom data to determine when a citizen needs additional phone-based or medical care follow-ups.

In stark contrast to contact tracing apps that have at best achieved 35 percent adoption, more than 91 percent of those who receive symptom-check text messages from Ottawa's system complete their surveys. At least 10 other public health departments have now adopted Ottawa's system through partnering with ImageSoft, the tech company that powers Ottawa's system.

This approach, blending technology with manual contact tracing, solves two key problems with contact tracing apps: trust and efficacy. Trust is a key foundation of public health and a big problem for contact tracing apps; my own research shows that people are divided on whom they trust to provide the apps as well as whether they trust the apps to actually work and to protect their data.

Beyond building trust, human contact tracers are also far more effective than apps. Contact tracers attempt to reach all citizens who have been exposed repeatedly—at multiple times a day, multiple days a week—until they make contact. In contrast, contact tracing apps rely heavily on people acting, unprompted.

For the apps to work, people need to voluntarily download the app, carry their phone with them when they leave the house, and upload their test results. This full reliance on citizens to not just comply with contact tracing but to participate actively risks leaving significant gaps in protection, especially if only a minority of the population adopts these apps, let alone properly uses them.

If contact tracing apps continue to fall short on adoption as the surge of cases increases, now is perhaps the time for big tech to remember that they need to listen to the public health experts these apps attempt to replace and to the public that has failed to adopt this new technology.

Rather than relying on inferring people's wants and needs from their data, tech companies need to engage those they serve directly and solicit the expertise they do not have. By partnering with public health departments and letting experts drive the innovation, tech companies can help keep contact tracers afloat rather than imposing solutions headed toward failure.

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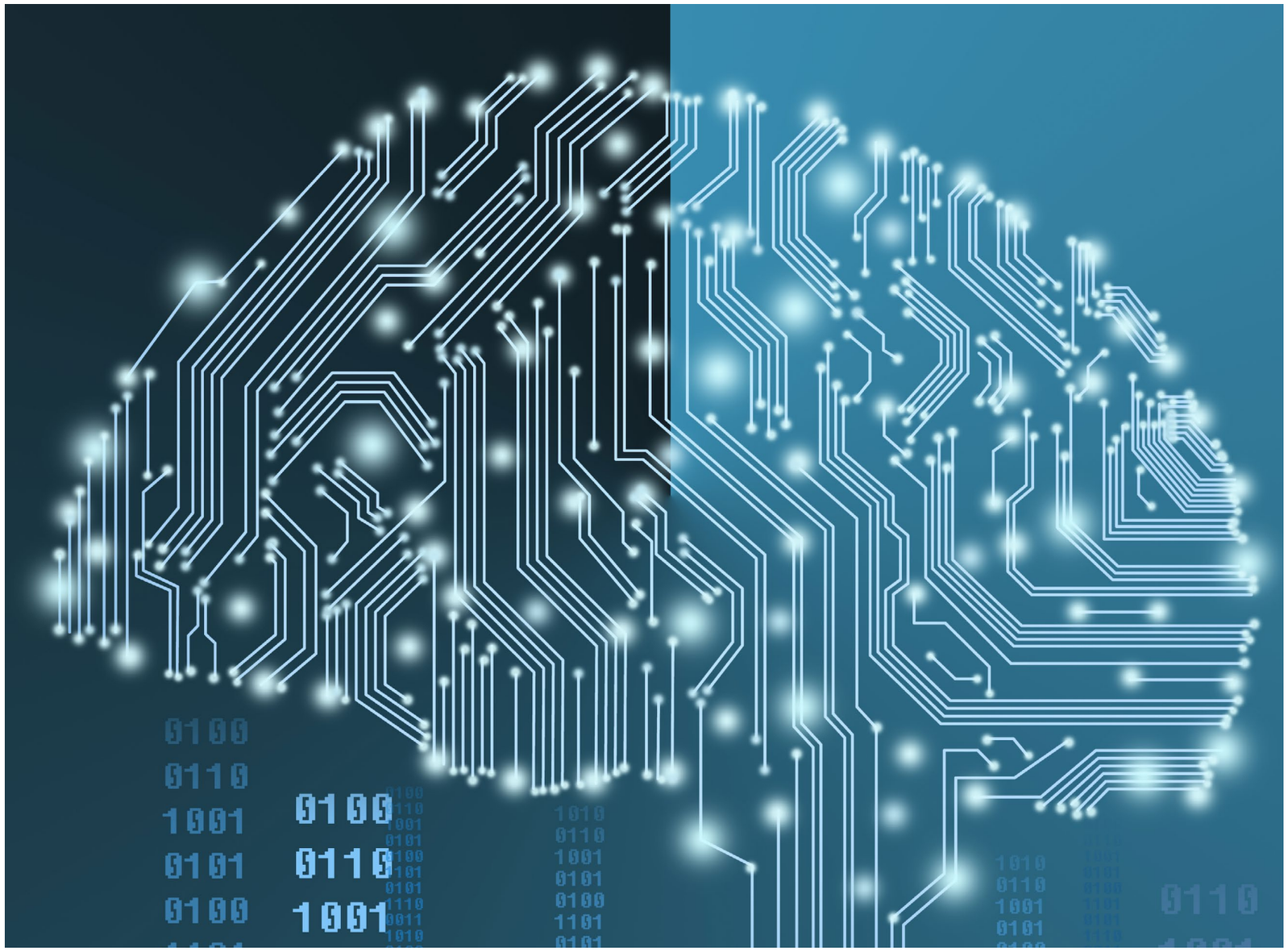
POLICY & ETHICS

Health Care AI Systems Are Biased

We need more diverse data to avoid perpetuating inequality in medicine



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Thanks to advances in artificial intelligence (AI) and machine learning, computer systems can now diagnose skin cancer like a dermatologist would, pick out a stroke on a CT scan like a radiologist, and even detect potential cancers on a colonoscopy like a gastroenterologist. These new expert digital diagnosticians promise to put our caregivers on technology's curve of bigger, better, faster, cheaper. But what if they make medicine more biased, too?

At a time when the country is grappling with systemic bias in core societal institutions, we need technology to reduce health disparities, not exacerbate them. We've long known that AI algorithms that were trained with data that do not represent the whole population often perform worse for underrepresented groups. For example, algorithms trained with gender-imbalanced data do worse at reading chest x-rays for an underrepresented gender, and researchers are already concerned that skin-cancer detection algorithms, many of which are trained primarily on light-skinned individuals, do worse at detecting skin cancer affecting darker skin.

Given the consequences of an incorrect decision, high-stakes medical AI algorithms need to be trained with data sets drawn from diverse populations. Yet this diverse training is not happening. In a recent study published in the

Journal of the American Medical Association, we reviewed more than 70 publications that compared the diagnostic prowess of doctors against digital doppelgangers across several areas of clinical medicine. Most of the data used to train those AI algorithms came from just three states: California, New York and Massachusetts.

Whether by race, gender or geography, medical AI has a data diversity problem: researchers can't easily obtain large, diverse medical data sets—and that can lead to biased algorithms.

Why aren't better data available? One of our patients, a veteran, once remarked in frustration after trying to obtain his prior medical records, "Doc, why is it that we can see a specific car in a moving convoy on the other side of the world, but we can't see my CT scan from the hospital across the street?" Sharing data in medicine is hard enough for a single patient, never mind the hundreds or thousands of cases needed to reliably train machine-learning algorithms. Whether in treating patients or building AI tools, data in medicine are locked in little silos everywhere.

Medical data sharing should be more commonplace. But the sanctity of medical data and the strength of relevant privacy laws provide strong incentives to protect data and severe consequences for any error in data sharing. Data are sometimes sequestered for economic reasons; one study found hospitals that shared data were more likely to lose patients to local competitors. And even when the will to share data exists, lack of interoperability between medical records systems remains a formidable technical barrier.

Whether by race, gender or geography, medical AI has a data diversity problem: researchers can't easily obtain large, diverse medical data sets—and that can lead to biased algorithms.

The backlash from big tech's use of personal data over the past two decades has also cast a long shadow over medical data sharing. The public has become deeply skeptical of any attempt to aggregate personal data, even for a worthy purpose.

This is not the first time that medical data have lacked diversity. Since the early days of clinical trials, women and minority groups have been underrepresented as study participants; evidence mounted that these groups experienced fewer benefits and more side effects from approved medications. Addressing this imbalance ultimately required a joint effort from the NIH, FDA, researchers and industry, and an act of Congress in 1993; it remains a work in progress to this day. One of the companies racing toward a COVID vaccine recently announced a delay to recruit more diverse participants; it's that important.

It's not just medicine; AI has begun to play the role of trained expert in other high-stakes domains. AI tools help judges with sentencing decisions, redirect the focus of law enforcement, and suggest to bank officers whether to approve a loan application. Before algorithms become an integral part of high-stakes decisions that can enhance or derail the lives of everyday citizens, we must understand and mitigate embedded biases.

Bias in AI is a complex issue; simply providing diverse training data does not guarantee elimination of bias. Several other concerns have been raised—for example, lack of diversity among developers and funders of AI tools; framing of problems from the perspective of majority groups; implicitly biased assumptions about data; and use of outputs of AI tools to perpetuate biases, either inadvertently or explicitly. Because obtaining high-quality data is challenging, researchers are building algorithms that try to do more with less. From these innovations may emerge new ways to decrease AI's need for huge data sets. But for now, ensuring diversity of data used to train algorithms is central to our ability to understand and mitigate biases of AI.

To ensure that the algorithms of tomorrow are not just powerful but also fair, we must build the technical, regulatory, economic and privacy infrastructure to deliver the large and diverse data required to train these algorithms. We can no longer move forward blindly, building and deploying tools with whatever data happen to be available, dazzled by a veneer of digital gloss and promises of progress, and then lament the "unforeseeable consequences." The consequences are foreseeable. But they don't have to be inevitable.

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