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December 2020–January 2021

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Layers of Risk

MULTIPLE AND COMPLEX UNDERLYING FACTORS DETERMINE WHY SOME PEOPLE GET TERRIBLY SICK FROM COVID-19

WITH COVERAGE FROM nature

LIZ TORMES

Slow Gains against the Virus

If we must find some good news about the global novel coronavirus pandemic, we perhaps could point to the improved survival rates recorded in the latest tallies—about 1.5 percent of diagnosed cases ending in death as of the beginning of November, compared with about 7 percent fatality during the spring's devastating first wave. Researchers have also assembled a clearer picture of what preexisting conditions dispose an individual to higher risk of death from COVID-19, which helps identify society's most virus-vulnerable populations.

In this edition's cover story ["Why Some People Get Terribly Sick from COVID-19"], journalist Claudia Wallis profiles these conditions and creates the compelling takeaway image of Russian nesting dolls, in which vulnerability to death is a complex equation: underlying roots, such as specific genes, are confounded by social and economic factors. Such insights haven't quite given humans an edge over this insidious virus, but we are slowly gaining ground. We hope you find many takeaways in this issue.

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Health & Medicine

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CHRIS GASH

On the Cover

Multiple and complex underlying factors determine why some people get terribly sick from COVID-19

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ALEX EDELMAN *GETTY IMAGES*

MAYANK MAKHIJA/NURPHOTO *VIA GETTY*

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ALEX EDELMAN *GETTY IMAGES*

COVID-19 Is now the Third Leading Cause of Death in the U.S.

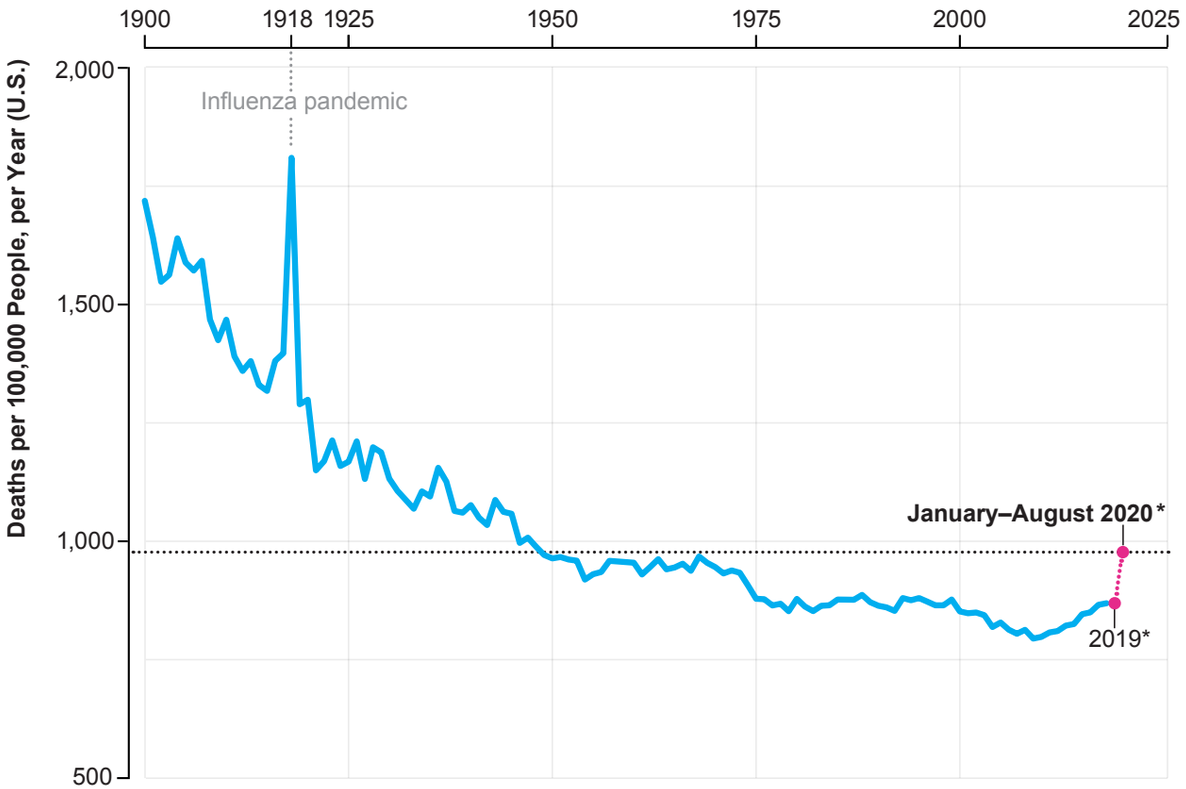
It kills more people than the flu, contrary to Trump's claims, and also surpasses stroke, Alzheimer's and diabetes

"It affects virtually nobody," President Donald Trump said of the novel coronavirus on September 21—a few hours before U.S. deaths from COVID-19 exceeded 200,000 and less than two weeks before he tested positive. Unlike the president, the numbers don't lie. The human toll underlying that milestone figure is a number about as big as the population of Salt Lake City or Birmingham, Ala.—and greater than the deaths in any U.S. conflict except for the Civil War and World War II.

The figures speak for themselves, and *Scientific American* takes a deeper look here. COVID-19 became the third biggest cause of deaths in the week of March 30 to April 4, trailing heart disease and cancer. It killed more people than stroke, chronic lower respiratory disease, Alzheimer's, diabetes, kidney disease or influenza. In that week, close to 10,000 people died of the illness caused by the

A Few Fateful Months Stymie Decades of Public Health and Medical Gains

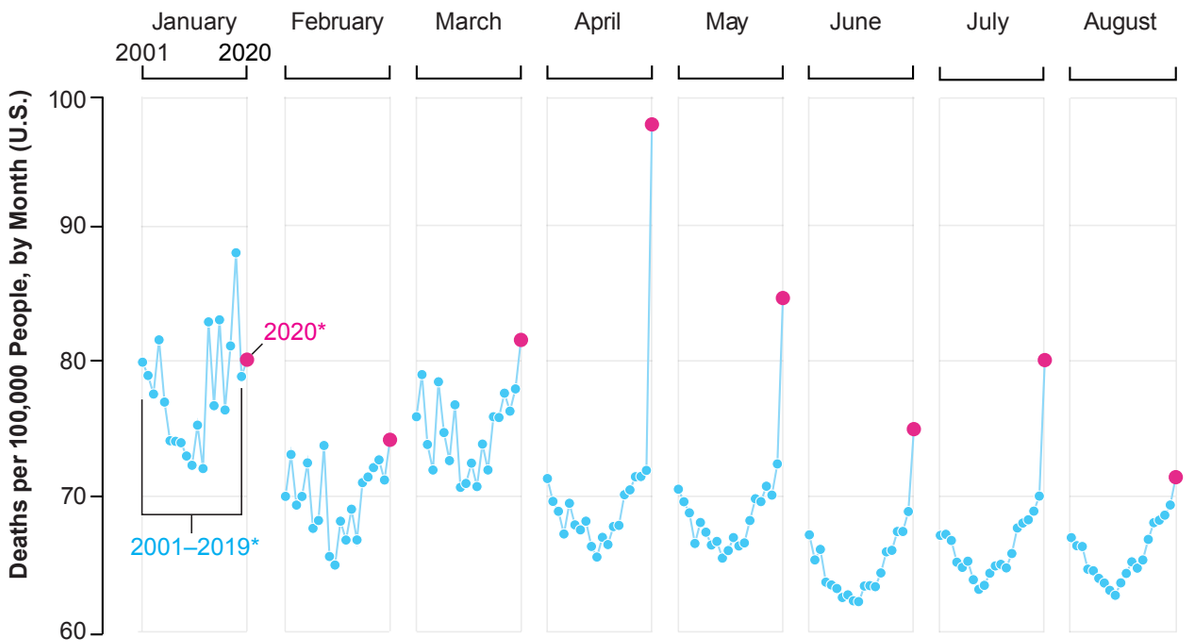
A larger share of the U.S. population died in the first eight months of 2020 than in any of the past 50 years, a period of declining mortality because of health-related improvements.



*The 2019 and 2020 figures are provisional and were likely undercounted in recent months. The rate for 2020 was calculated by annualizing the data count of January through August. Older populations die at a higher rate, and COVID-19 has been impacting such populations more than younger ones. So the age adjusted-rate for 2020 will likely be lower than the crude rate data shown here (more than 940 deaths per 100,000 people).

April Was the Cruelest Month as COVID-19 Became Exponential

The U.S. experienced the highest monthly death rate of the past two decades in April 2020. Rates dropped in May and June, then began climbing up again in July.



*The 2019 and 2020 figures are provisional and were likely undercounted in recent months.

coronavirus. The flu, which Trump and others have invoked when discussing COVID-19, led to 1,870 deaths (a figure that includes pneumonia) over the same time frame. A spike in the week-by-week accounting came in mid-April, when COVID-19 cases became the leading cause of death. The disease returned to the third deadliest spot in the week of May 4 to 9 and has stayed there since.

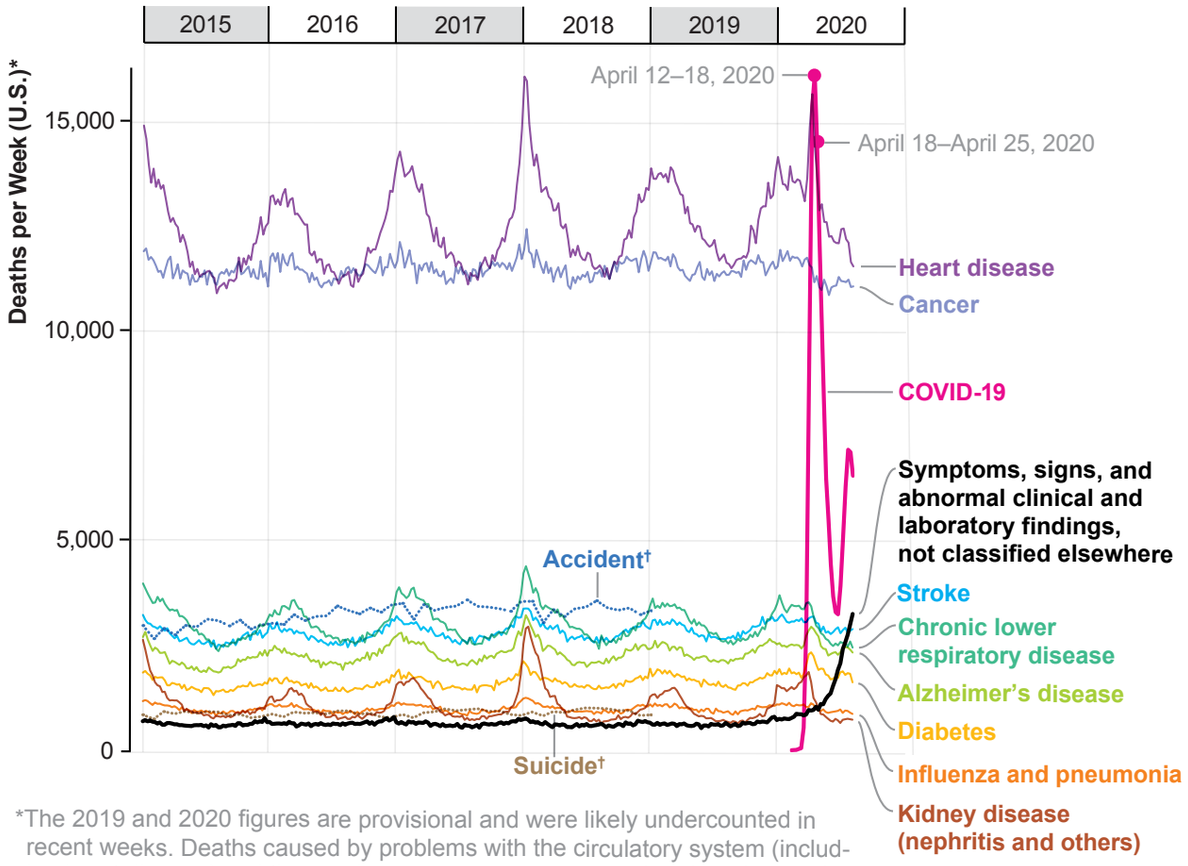
This profile of loss can be broadened further to measure excess deaths above typical mortality rates. Provisional death counts from the Centers for Disease Control and Prevention show that more people died every month from March to August this year than during the same period in the past 20 years. (The statistics include deaths from both the virus and upticks for other causes such as a lack of medical care as hospitals became overwhelmed.)

COVID-19 marks at least a temporary setback for epidemiology. The share of Americans who died in the first eight months of this year was greater than that of any year going back to 1970—a year that paradoxically turned out to be a good one for public health. In 1970 President Richard Nixon signed the Occupational Safety and Health Act, put his signature on a bill to ban television and radio cigarette ads, and sent to Congress a plan for setting up the

YOUYOU ZHOU; SOURCES: U.S. CENSUS; CENTERS FOR DISEASE CONTROL AND PREVENTION, AND NATIONAL CENTER FOR HEALTH STATISTICS

COVID-19 Outpaces Stroke, Alzheimer's and Diabetes as a Killer

This chart shows deaths per week for the top 10 causes of mortality—per 2017 annual rankings—plus COVID-19 and a provisional category for abnormal clinical and lab findings. (That category includes cases pending COVID-19 test confirmation, and it may be revised later by public health officials.) For two weeks in April, more Americans died from COVID-19 than heart disease.



*The 2019 and 2020 figures are provisional and were likely undercounted in recent weeks. Deaths caused by problems with the circulatory system (including heart disease) and the respiratory system are seasonal and tend to peak in cold winter months.

† Deaths caused by accidents and suicide are rooted in monthly reports. Data are not available for 2019 and 2020.

Environmental Protection Agency. Maybe such actions can serve as precedents in years ahead when policy makers convene to plan for the inevitability of future pandemics.

—Gary Stix and Youyou Zhou

When and Why You Should Get a Flu Shot

Experts explain why getting vaccinated is important every year—and especially during a pandemic

As the U.S. continues to grapple with the novel coronavirus pandemic, another infectious respiratory disease is already looming: influenza. Flu season typically begins around November in the Northern Hemisphere, and the combined burden of the illness and COVID-19 could overwhelm hospitals and testing sites. The good news is that a safe and effective flu vaccine is already available to everyone aged six months and older.

"The answer to the question 'Why should you get a flu vaccine?' is the same this year as it is every year. But there are some additional reasons why it's extra beneficial to get [it] this year," says Emily Landon, executive medical director of infection prevention and control at the University of Chicago Medicine. She explains that influenza can have dire consequences ranging from loss of productivity to death. "You should do everything you can to prevent the flu, and the shot is the best way we can do that," Landon says. In addition to protecting yourself, a flu shot also helps protect other family members who may be more vulnerable to respiratory disease, she notes.

The U.S. Centers for Disease Control and Prevention estimated that in the 2018–2019 season, some 35.5 million Americans came down with the flu and that about 34,000 of them died from it. Flu shots prevented another 4.4 million cases and about 3,500 deaths. In 2020 vaccinating as many people as possible against influenza could be critical to preventing a dual-epidemic scenario. But getting a flu shot is good policy in any year, experts say.

"In this COVID-flu season that's coming, it's even more important to get a flu shot because it's going to be hard to tell the difference between flu and COVID," considering that the two diseases have similar symptoms, Landon says. Because of that problem, people who get the flu might needlessly stay quarantined or get tested for COVID-19 as a precaution. Therefore, widely vaccinating against influenza can reduce unnecessary

YOUYOU ZHOU; SOURCES: CENTERS FOR DISEASE CONTROL AND PREVENTION, AND NATIONAL CENTER FOR HEALTH STATISTICS

COVID-19 testing and protect vulnerable people: those whose immune symptoms have been compromised by either of the two illnesses are at greater risk of contracting a more severe case of the other one. "Anything to do with reducing the risk of respiratory disease is going to be important," Landon says.

In the global south, the peak of each flu season occurs during winter, which allows epidemiologists to predict the disease's severity during the Northern Hemisphere's upcoming winter. This year the flu season in the Southern Hemisphere was relatively mild—possibly as a result of COVID-19 precautions, says James Cherry, a pediatric infectious disease physician at the University of California, Los Angeles. "This year was an incredibly light year," likely because social distancing and mask wearing kept influenza from gaining a "foothold," he says. "That may well happen here, so we can probably expect a mild flu season. But nevertheless, we should all get our vaccine."

Is there an optimal time to get a flu shot? Stuart Ray, an infectious disease physician at the Johns Hopkins University School of Medicine, says everyone aged six months and older should get a vaccine every flu season, preferably before Halloween. "It takes some time for your immune system to recognize and respond to the vaccine, and those responses last for a long time," he says. On average, the antibodies produced by an individual's immune response to a flu shot take two weeks to develop and, although there is no definitive time line, can last for about four to six months—given that a person's immunity depends on many factors, from their own immune system function to the virulence of the flu strain. And the immune system can maintain a "memory" of the vaccine for more than a year that can "reawaken and contribute to protection against a severe infection," Ray adds.

Landon agrees that there is no reason to put off getting vaccinated for influenza. "Wherever it's convenient to you to get a flu shot, you should absolutely get a flu shot," she says. "If you have a doctor's visit or if your kids have a well-child visit coming up, now's the time to get it." But Landon adds that social distancing and reductions in holiday travel could make this year's flu season peak slightly later than usual. "It may be after we start getting people vaccines for COVID that we see more resurgence of influenza" because of resulting declines in social distancing, she says. "You may want your flu vaccine to last more into the spring. And if you want peak effectiveness in February, March and April, then you probably shouldn't get it until October or November."

If COVID-19 precautions also dampen the spread of influenza, would it be a good idea to start wearing masks every flu season? The answer is maybe. "I think a more important thing is to see that everybody gets vaccinated," Cherry says. Landon notes that since the 2003 SARS epidemic struck Asia, mask wearing has become far more commonplace there. The same trend might catch on elsewhere—which would be wise, she says. "That's something medical science has been pushing for a long time, but it's not been culturally a thing in the United States," Landon says. "But I think it should be."

All three experts agree on the bottom line: make a plan to get a flu shot to protect yourself and those around you. "While we don't have a vaccine for SARS-CoV-2, we do have tools to limit the impact of influenza," Ray says. "And we all need one less thing to worry about in 2020."

—Jim Daley

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New Tinnitus Treatment Alleviates Annoying Ringing in the Ears

A noninvasive device designed to rewire brain circuits reduced symptoms of tinnitus in a large, exploratory clinical trial

Tinnitus, the perception of phantom noises in the absence of actual sound, affects millions of people around the world. According to one recent assessment, approximately one in 10 adults in the U.S. experiences tinnitus—and in nearly a quarter of these individuals, symptoms last for more than 15 years. Those with tinnitus can also experience complications such as difficulty focusing, fatigue, anxiety and an overall reduction in the quality of life.

Psychological interventions such as cognitive-behavioral therapy can help lessen the distress, but to date, no drug or medical device has been shown to reliably improve this condition. Now researchers have inched closer to making a treatment for tinnitus a reality. According to a new study, published in October in *Science Translational Medicine,* a noninvasive device that applies a technique known as bimodal neuromodulation, combining sounds with zaps to the tongue, may be an effective way to provide relief to tinnitus patients.

According to study co-author Hubert Lim, an associate professor of biomedical engineering and otolaryngology at the University of Minnesota, this treatment targets a subset of brain cells that are firing abnormally. Through studies in both humans and animals, Lim's team and others previously reported that electrically stimulating touch-sensitive neurons in the tongue or face can activate neurons in the auditory system. Pairing these zaps with sounds appears to rewire brain circuits associated with tinnitus.

The technique developed by Lim and his colleagues is designed to promote the activation of brain circuits in response to many different sounds to drown out phantom noise. "The idea is that eventually your brain gets sensitive to many different things," Lim explains. "In a way, you have suppressed the tinnitus neurons but only by elevating the other neurons." Another group led by Susan Shore, a professor of otolaryngology at the University of Michigan, developed a similar device with a different approach: instead of increasing sensitivity to a broad spectrum of sounds, the team's method pairs a sound that matches the phantom one heard by patients with a specifically timed electrical pulse to the head or neck. In a 2018 study that included 20 people with tinnitus, Shore's team reported that this technique was effective in reducing the loudness and intrusiveness of the subjects' tinnitus. "You can think of it as two ways to treat tinnitus," Lim says. "One is you can try to find [the tinnitus cells] and shut them down. Our approach is to make everything in the auditory system much more hyperactive to everything but the tinnitus."

To examine the efficacy and safety of their device, Lim and his colleagues conducted a randomized, double-blinded exploratory study with 326 adults who had chronic tinnitus at two sites: St. James's Hospital in Ireland and the Tinnitus Center at the University of Regensburg in Germany. Participants were instructed to use the device for 60 minutes daily for 12 weeks. They were divided into three groups—each of which received slightly different treatments that varied by the type of sound used, the timing of electrical pulses, and the delay between the sound and the stimulation. The study was funded by Neuromod Devices, a Dublin-based company, where Lim is chief scientific officer, that is devel-

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oping and selling the bimodal neuromodulation device.

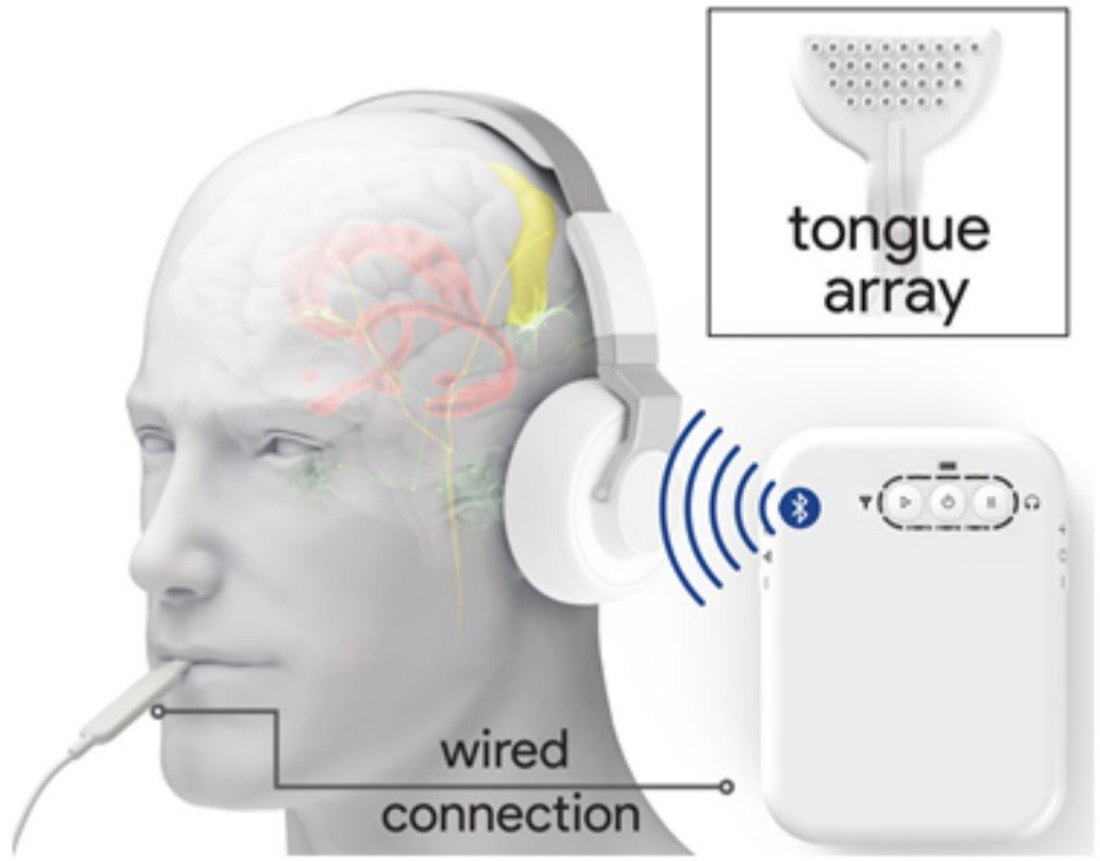
Results showed that 84 percent of participants completed the 12-week regimen. Afterward, approximately 81 percent of treatment-compliant participants exhibited improvement in psychosocial variables such as the ability to concentrate or sleep, along with lower levels of anxiety and frustration and better quality of life. In around 77 percent of the group, this improvement persisted a year later. Also, 66 percent of participants reported feeling that they had benefited from the device. There were no significant differences in these measures among the three groups.

"The study is very thorough and comprehensive," says Richard Tyler, an audiologist at the University of Iowa, who was not involved in the new study. "Given that, at this point, there is no pill or no surgery available for tinnitus, this work is very important." He adds that the investigation had some notable shortcomings, however. The most concerning was the lack of a control condition in which some participants would not receive any therapeutic stimulation to rule out placebo effects. Another limitation was that the authors did not report whether the subjects experienced a reduction in tinnitus—actual changes in the perceptions of the phantom sounds. "You have tinnitus, and you have your reactions to tinnitus. Those are two different things," Tyler says. "If you're going to try and decrease the tinnitus, then you should be measuring the tinnitus."

According to Lim, his group chose to focus on how the study participants reacted to tinnitus because patients' auditory perceptions may vary, depending on how they are affected by the condition. The team did, however, measure perceptual changes and plans to present those findings in a subsequent paper.

"I was impressed with the improvements measured in the patients," says Rilana Cima, a psychologist at Maastricht University in the Netherlands, who was not involved in this research but is currently collaborating with some of the co-authors on another study.

Although the approach seems promising, it would be useful to see whether a group unaffiliated with the company developing the device would be able to replicate these results, Cima adds. "I would advise, before we start producing these things en masse, to do that first."



Neuromodulation device to alleviate tinnitus delivers sounds while an electrode array stimulates the tongue.

Neuromod's bimodal neuromodulation device is currently available through physicians in Ireland and Germany for prices from €2,500 to €2,750 (around $2,900 to $3,200). According to Lim, the company is also seeking approval from the Food and Drug Administration to make the treatment available in the U.S. His group also plans further experiments to examine the mechanism underlying its effectiveness. "At this stage, we can say that bimodal stimulation is changing things in the brain," Lim says. "The next step is to do brain imaging [in humans] and animal experiments to really figure out what has changed in the brain."

—Diana Kwon

FROM "BIMODAL NEUROMODULATION COMBINING SOUND AND TONGUE STIMULATION REDUCES TINNITUS SYMPTOMS IN A LARGE RANDOMIZED CLINICAL STUDY," BY BRENDAN CONLON ET AL., IN *SCIENCE TRANSLATIONAL MEDICINE*. PUBLISHED ONLINE OCTOBER 7, 2020

Why Some People Are Still Getting Sick–but Not with COVID

Despite pandemic precautions, the common cold and other illnesses are still circulating

On September 18 Orianna Carvalho woke up at 3 A.M. with a sore throat and the sniffles. At first, she thought her symptoms were caused by allergies. But as the minutes ticked by, she began to worry they were caused by COVID-19. The following morning Carvalho got tested at the University of Rhode Island, where she is a first-year doctoral student. Over the next few hours she developed a fever, and the catastrophizing began in earnest. When Carvalho finally learned that the cause of her misery was not COVID but the common cold, she was relieved but also surprised. "I have been so careful—wearing a mask every time I go somewhere, keeping at least six feet away from other people, using hand sanitizer and washing my hands," she says. "I don't know how I got sick."

Carvalho is not alone. Many Americans have been puzzled to find that their best efforts to avoid COVID-19 have not always protected them from less troubling infections such as colds, stomach bugs and strep throat. How have other pathogens slipped through our anti-COVID defenses? There are no clear-cut answers, but the work of infectious disease specialists, virologists and epidemiologists—much of it conducted decades before the current pandemic—provides some clues. Their research shows that many microbes are more numerous, hardy and contagious than SARS-CoV-2, the virus that causes COVID-19. And for many of us, even our best efforts are not good enough.

The public health measures taken to stem the spread of SARS-CoV-2, which as of late October had been responsible for the deaths of more than 229,000 people in the U.S., have also affected the prevalence of other respiratory viruses. This year the Southern Hemisphere essentially skipped flu season, which typically hits countries such as Australia, Chile and South Africa in May or June. Data from Australia suggest that although pandemic restrictions pushed many non-flu viruses out of circulation, a group of cold-causing pathogens known as rhinoviruses stuck around. A similar trend could be in store for the U.S., according to researchers who are tracking transmission of respiratory viruses in New York State, Washington State and Texas. Pedro Piedra, a pediatric infectious disease specialist at the Baylor College of Medicine, says that although he has seen a significant decrease in many common respiratory viruses during the pandemic, he has noticed an uptick in rhinoviruses this fall.

Some virologists believe that the

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sheer number of viruses that cause the common cold can make it exceedingly difficult to avoid catching one: there are around 200 different pathogens. These include four coronaviruses (the group that includes SARS-CoV-2); four parainfluenza viruses (which, despite their name, bear no relation to influenza viruses); respiratory syncytial virus; and 160 different rhinoviruses. Viral censuses have revealed that dozens of these rhinoviruses circulate in any one place at a given time. "You might be immune to the flu, but you are not going to be immune to all those rhinoviruses," says James Gern, a rhinovirus researcher at the University of Wisconsin–Madison. "That's one unique feature of rhinoviruses—you are always going to be susceptible to some."

But there is only one SARS-CoV-2 virus, and it has proved to be more than enough to wreak havoc on our lives. The persistence of rhinoviruses during the pandemic may be the result of not only their impressive number but also their primitive nature, says Ian Mackay, a virologist at the University of Queensland in Australia. Similar to the flu virus, SARS-CoV-2 is a more highly evolved virus that is enclosed in a fatty "lipid" membrane. This envelope can cloak the pathogen from antibodies deployed by the human immune system, enabling it to infect cells undetected. But it can also break down after exposure to the environment or a good handwashing, rendering the virus harmless. Rhinoviruses, on the other hand, never evolved an envelope. These so-called naked viruses, which also include the gut-distress-inducing noroviruses, are more resistant to sanitizers and disinfectants and may last longer on fingertips and surfaces.

Although it is possible to pick up respiratory viruses from contaminated surfaces, most experts say we are more likely to get sick through contact with infected people. In 1969 half of a group of men wintering at a remote Antarctic base developed signs and symptoms of the common cold after being isolated for 17 weeks. Scientists never identified the source of the outbreak, but Mackay and others think it is possible that the men entering the base might not have been as healthy as they looked. Asymptomatic spread has gotten a lot of attention during the COVID-19 pandemic: studies

"You might be immune to the flu, but you are not going to be immune to all those rhinoviruses."

—James Gern

suggest 40 to 45 percent of SARS-CoV-2 transmission comes from people not yet showing symptoms. Many colds and flus may also be passed along by people who do not have symptoms, although to what extent this spread occurs is an open question. At least one study detected rhinoviruses in a third of asymptomatic children.

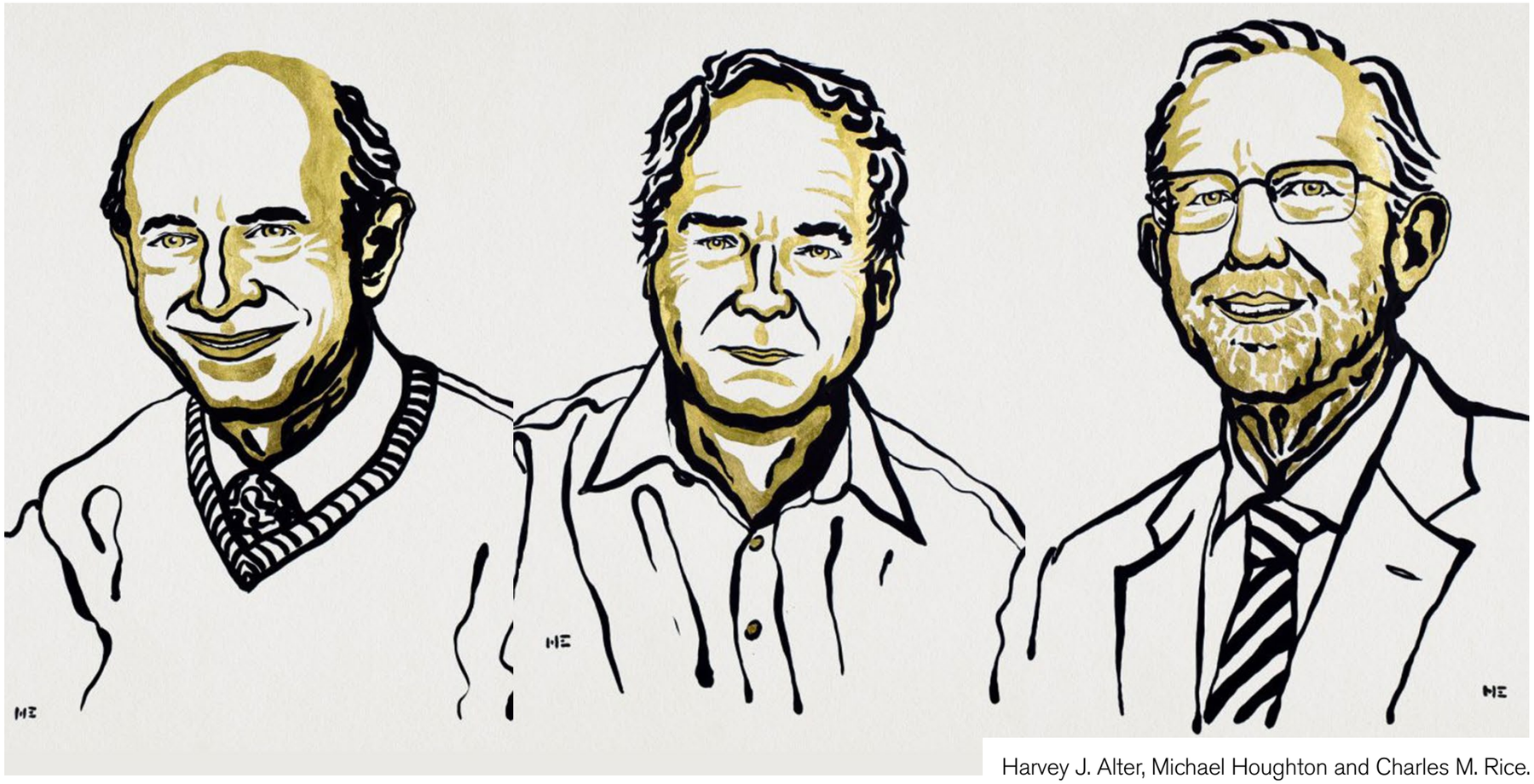
"Children, in particular, are a petri dish for transmission," says Arnold Monto, an epidemiologist at the University of Michigan, who studies the spread of respiratory illnesses within households. Because kids are prone to eye rubbing and nose picking, they can quickly contaminate their home with a menagerie of viruses and bacteria. Unlike the acute respiratory infections that typically come and go in a matter of weeks, children can harbor chronic infections with bacteria—such as *Streptococcus pyogenes*, which causes strep throat—for months before ever making themselves or others sick. Tara Smith, an epidemiologist at Kent State University, says it is unclear how such bacteria move from harmless colonizer to invasive pathogen, but the stress of the pandemic could play a role. And kids are not the only germ factories in our homes: pets are common carriers of many pathogens. "People probably get sick from their animals more than we realize," Smith says.

Despite the myriad possibilities, many experts believe the explanation for why some of us are still getting routine infections is fairly mundane. "Some people may think they are better protected than they actually are," Smith says. Gern agrees: "If cold viruses are still spreading, that means we are still having person-to-person contact," he says. We live in a world where once beneficial actions—such as hugging a friend or going to the gym—now pose heightened risks to our health. For her part,

Carvalho thought she was doing everything she could to be safe. After months of staying home, she returned to the gym for some socially distanced martial arts. She now suspects that it is how she got sick.

Since the beginning of the pandemic, more than 80,000 people who wondered if they had a COVID infection have called the telemedicine company Doctor on Demand, according to Prentiss Taylor, a physician and the company's vice president of medical affairs. More than half of those cases were not referred for COVID-19 testing, because some other respiratory affliction was deemed more likely. Under the circumstances, catching a cold instead of COVID might feel like dodging a bullet.

But the fact that other viruses have been able to slip through our defenses could serve as a warning for future pandemics, Mackay says. "If we ever see a new rhinovirus come along, we will have even more trouble containing it than SARS-CoV-2. A rhinovirus pandemic would be a massive threat that would spread like that," he adds, snapping his fingers. "And there's no guarantee it would only cause common colds." —*Marla Broadfoot*



Harvey J. Alter, Michael Houghton and Charles M. Rice.

NIKLAS ELMEHED, © NOBEL MEDIA

Discovery of Hepatitis C Snags Nobel Prize in Medicine

Harvey J. Alter, Michael Houghton and Charles M. Rice share the award for identifying the virus behind the blood-borne liver disease

This year's Nobel Prize in Physiology or Medicine was awarded for the discovery of the hepatitis C virus, which causes severe liver disease and chronically infects more than 70 million people worldwide. The prize was jointly awarded to American researchers Harvey J. Alter and Charles M. Rice and British-born scientist Michael Houghton.

Three hepatitis viruses are known to infect the liver: Hepatitis A is transmitted by water or contaminated food, and it causes a short-term infection that is typically resolved within weeks. Hepatitis B and C are transmitted by contaminated blood, and they cause chronic infections that can silently attack the liver for decades. This damage can lead to cirrhosis or liver cancer, which are sometimes only treatable

through liver transplants. As a result of hepatitis C's discovery and blood-screening programs, the virus has been nearly eliminated, and most cases are treatable.

"I'm surprised but not that surprised" about the Nobel announcement, says Timothy Sheahan, a virologist and an assistant professor of epidemiology at the University of North Carolina at Chapel Hill's Gillings School of Public Health. Sheahan did his postdoctoral work on hepatitis C in Rice's laboratory at the Rockefeller University. "Charlie Rice's work in discovering the hepatitis C virus and creating systems to study the biology and do drug discovery for [the virus] led to the development of antiviral drugs that can cure people of hepatitis C. The same effort … led to the discovery and use of what is now called remdesivir," an antiviral drug that has been shown to shorten the duration of COVID-19, adds Sheahan, who has studied the medication's effectiveness against SARS-CoV-2 and other coronaviruses. "And now this is being used on the president of the United States."

Hepatitis B and C were first noticed in patients who had received numerous blood transfusions or therapeutics made from donated blood. In the mid-1960s American physician Baruch Blumberg discovered the hepatitis B virus (for which he was awarded the 1976 Nobel Prize in Physiology or Medicine). But this virus did not explain all cases of post-transfusion liver disease. In the late 1960s Alter, who was then working at the National Institutes of Health Blood Bank, began to suspect an as yet unknown pathogen was causing the disease. He later showed that the illness could be transferred to monkeys from patients' blood.

Isolating the hepatitis C virus was harder, but Houghton—then working at the pharmaceutical company Chiron—and his colleagues were able to successfully clone it in 1989 by introducing viral DNA from an infected animal into bacteria and using human antibodies to the virus to screen for its genetic sequence. They found that hepatitis C resembled viruses from a family called flaviviruses. It was the first time this type of molecular biology approach had been used to identify a virus. The discovery led to a blood test that could screen for hepatitis C. This immediately reduced the number of cases resulting from blood transfusions worldwide.

But one question remained: Did the virus alone cause disease? Rice, then at Washington University in St. Louis, and his colleagues cloned the pathogen and injected the copies into animals, but the virus did not replicate. When Rice compared the sequences of many viral clones, he saw they contained genetic mutations that made them defective. But when he repaired the mutations, the clones caused clinical signs of hepatitis C in chimpanzees. This result showed that the cloned virus could cause disease.

Rice says he was not expecting the award, "and I'm still not!" His first reaction to hearing the phone ringing in the living room at 4:30 A.M. was "not good," he says. He figured it was either a wrong number or a telemarketer. "The secretary of the [Nobel] Committee, with a slight Swedish accent, was on the line. And I sort of thought it might be a crank phone call," Rice says. "He said that if I didn't believe him, I should watch this event that was going to take place at 11:30 Swedish time. And so I did."

Rice did not intentionally set out to study what is now called hepatitis C. At the time, he was studying yellow fever virus, which is also a flavivirus but is very different from the hepatitis C virus. When Alter and Houghton published seminal papers on a

"It really puzzles me that the Nobel Committee says they are awarding the best science, but the reality is: there are lots of people contributing to the best science who are women and people of color. They could do more to address that disparity."

—Angela Rasmussen

mysterious hepatitis virus in *Science* in 1989, Rice was intrigued. "This was a new virus, at least in terms of being able to study it," he says. "It started off as a small side project that really nobody in lab was excited about." Scientists could not even grow the virus in cells. From there, Rice's team built on the work of Houghton and his colleagues to help flesh out the pathogen's genome sequence, clone the viral RNA and infect animals with it, ultimately demonstrating that the hepatitis C virus alone was the cause of the disease.

"I think Alter truly deserved it," says Patrizia Farci, chief of the hepatic pathogenesis section at the National Institute of Allergy and Infectious Diseases, who has been collaborating with him for years. "This work, together with [that of] Michael Houghton and Charlie Rice, has saved millions of lives and also shows that science does not have any barrier." Farci says she first met Alter in the 1980s, and she says he used to write and read poetry about science. "He's not only science!" she adds.

"This was a new virus, at least in terms of being able to study it. It started off as a small side project that really nobody in lab was excited about."
—Charles M. Rice

Sheahan speaks similarly highly of Rice. "He's just a special person," Sheahan says. "I've had two mentors, [including Rice]. They're both really smart. But these are famous people who are actually good at being humans."

"All three laureates have made tremendous contributions," says Angela Rasmussen, a virologist and an associate research scientist at the Columbia University Mailman School of Public Health. Rasmussen, who did her postdoctoral work on the hepatitis C virus (but not with Alter, Houghton or Rice). She admits she was a bit surprised that the award went to this area of research. although she says it is very relevant to the COVID-19 pandemic because hepatitis C is also a global disease.

While Rasmussen says the recipients are all deserving, she notes that the Nobel Committee members have once again honored three white men with the prestigious award. "It really puzzles me that the Nobel Committee says they are awarding the best science," she says, "but the reality is: there are lots of people contributing to the best science who are women and people of color. They could do more to address that disparity."

Last year's prize was awarded to scientists William Kaelin, Jr., Peter Ratcliffe and Gregg Semenza for the discovery of how cells sense oxygen.

—Tanya Lewis

Why Some People Get Terribly Sick from COVID-19

Beyond factors such as age and sex, underlying aspects of biology and society influence disease severity

By Claudia Wallis

CHRIS GASH

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YOU MIGHT HAVE A SNIFFLE AND BE DONE. YOU MIGHT RUN a fever with a cough and unshakable fatigue for five days—or 10. Or you might end up in a hospital, gasping air into congested lungs, an immunological storm raging in your body. And you might not make it through COVID-19 alive.

What determines if someone gets desperately ill from the disease that is ripping its way across the planet? You are likely familiar with the broad categories of people who face greater risk: older individuals, men, those who have certain chronic conditions, and—notably in the U.S. and England—people of color. But researchers are looking deeper into these groups to determine the underlying roots, both biological and social, for their vulnerability. Investigators are relating age-related risk to the ways that the immune system changes over the years, for example, and examining male-female differences in immune responses. Some scientists are probing for genetic variations that might raise susceptibility. Others are highlighting the social, environmental and economic factors that elevate risk, including racism.

For a given individual, the elements of risk stack up like the layers of a Russian nesting doll. The innermost core includes genes, biological sex and age. Cellular and hormonal factors that accompany these characteristics affect vulnerability to infectious microbes, including SARS-CoV-2, the coronavirus that is causing the pandemic. The second layer consists of diseases and chronic conditions acquired over time, many of which make it easier for the virus to enter cells or harder for the body to fight it effectively. The outermost layer reflects the accumulated nicks and gouges of external circumstance: housing and work conditions, poor access to health care, nutritional status, and exposure to toxins and pollution. For people of color, these social and economic aspects include the cumulative stresses of systemic racism and discrimination.

These layers are not independent. With aging, for example, comes more chronic disease and, too frequently, a decline in living conditions such as housing, social support and food security. Nor are all the contributing risk factors known for an infection that emerged little more than eight months ago. Still, by applying existing science to emerging data about the features that make up these layers, researchers say, one can begin to make sense of COVID-19's dramatic range of severity.

HOW AGE IMPACTS IMMUNITY

Age is probably the single biggest determinant of how sick someone gets from the coronavirus. In China, where the pandemic began, the average person with a confirmed infection had a 2.3 percent chance of dying. But for people between the ages of 70 and 79, it was 8 percent, and for those older than 80, it was 14.8 percent. In New York City, nearly half of confirmed deaths were among the elderly, aged 75 and older, and another quarter were among those aged 65 to 74. An analysis of 17 million people in England, published in *Nature* in July, concluded that patients older than 80 were at least 20 times more likely to die of the infection than those in their 50s.

"Age was our biggest predictor of outcome," says Mangala Narasimhan, regional director of critical care at Northwell Health, the largest health-care provider in the New York City area, and a co-author of a report in *JAMA* on the characteristics of 5,700 hospitalized COVID-19 patients. The dense concentration of elderly people in nursing homes, where infections can spread quickly and prevention is often inadequate, is clearly one reason for this correlation. But biology is another factor, particularly the aging of the immune system.

As the decades roll by, the human body becomes less effective at fighting infections. This decline is one reason why roughly 90 percent of U.S. deaths from influenza are among people aged 65 and older and why vaccines are less protective in the elderly. Basically our defensive cells become thinned out in number and variety. And like

old warriors, they become more geared toward fighting yesterday's battles with familiar enemies than tackling something new, such as the latest flu strain or the novel coronavirus.

With age, B cells, which make antibodies, and T cells, some of which directly kill infected cells and some of which alert the B cells, are no longer produced in large quantities in the bone marrow and thymus gland, respectively. Eventually production nearly grinds to a halt. "It goes from a fire hose at eight years old to a leaky, dripping faucet when you are 80," explains immunologist Kenneth Dorshkind, a professor of pathology and laboratory medicine at the University of California, Los Angeles. Older adults maintain populations of these essential immune cells in the lymph nodes and spleen, but "they develop defects with age, so they don't function as well," he says.

For example, as people age, both the stem and arms of the Y-shaped antibody molecule become less flexible. This limits the body's ability to modify them to match an unfamiliar invader. As a result, antibodies may not lock on as effectively. T cells, meanwhile, lose a lot of the variety of receptors that allow them to respond to diverse pathogens, and they may lack the vigor to rapidly multiply in response to infection, says Jörg Goronzy, an immunologist who studies T cell aging at Stanford University. "Healthy old people have lost at least 75 percent of their T cell receptor repertoire," he estimates. "At one point, we may lack the receptors that have an optimal fit" for the invading microbe.

Older people are also far more prone to chronic diseases that involve low-grade inflammation, which seems to further compromise the immune system. Goronzy says it is unclear whether a geriatric immune system resorts to more inflammation to protect the body or whether the inflammation comes first and impairs defenses. He suspects it is a combination of the two. Both he and Dorshkind predict that if a coronavirus vaccine becomes available, it will probably be less protective for aged people. As with the flu shot, an extra strong dose or some kind of booster may be needed.

"Healthy old people have lost at least 75 percent of their T cell receptor repertoire. At one point, we may lack the receptors that have an optimal fit for the invading microbe."
—Jörg Goronzy

WHY MEN FARE WORSE

Sex also contributes to COVID-19 severity: men are roughly twice as likely to die of the infection as women, although the gender gap varies somewhat from place to place. In Italy, for example, 70 percent of those who died by this spring were men; in the U.S., the figure was 59 percent. Whether men are also more likely to acquire the infection is unclear because of biases and country-by-country discrepancies in who gets tested for the virus. But globally "the death rate data are more robust and consistent," says molecular biologist Sabra Klein, co-director of the Johns Hopkins Center for Women's Health, Sex and Gender Research.

Klein sees three plausible biological factors in women's relative survival. First, the female immune system is simply stronger at just about every level, partly because female estrogen hormones tend to amp up the immune system, whereas male androgen hormones tend to dial it back. (A hypervigilant system is a double-edged sword for women, who pay a price by having a greater risk of autoimmune diseases.)

"When the female immune system sees a virus, we tend to mount a much more rapid response, and the magnitude is often greater," Klein says. This advantage, which includes antibody response, has been shown with other infections and reactions to vaccines and in mouse models of the earlier SARS coronavirus, which also killed more men than women. Women may have evolved a stronger immune system to allow for antibodies, intercell signals called cytokines and other defense mechanisms to be passed to their babies in utero and through breast milk.

A second factor in the sex gap, Klein says, is that "as they start to hit their 50s and 60s, men have more of the underlying conditions—heart disease, hypertension, diabetes"—that worsen coronavirus outcomes. Women tend to develop these ailments somewhat later, which could help explain why the discrepancy between male and female mortality in the U.S. appears largest in the 45-to-64 age range.

A third possible contributor is differences between genes on the female X and male Y sex chromosomes. "It turns out that there are more than 60 genes associated with immune function on the X chromosome," Klein says. Some are involved in the production of interferons, key modulators of the body's response to viruses. "My group and others have shown that females show greater expression of some of these genes than do males," Klein adds, "and this can have functional significance."

Behavior may also factor into the higher male death rate. In many cultures, men are more likely to smoke—a habit linked to a worse prognosis. Women, in contrast, are inclined toward more protective conduct. They were about 50 percent more likely than men to wear a face mask, wash their hands and avoid public transit during earlier respiratory disease epidemics such as bird flu and SARS, according to a 2016 meta-analysis by Kelly Moran and Sara Del Valle, both at Los Alamos National Laboratory. Such gender differences in attitude and behavior have continued in the current pandemic, according to a survey conducted in March and April by the National Bureau of Economic Research. Responses from 21,649 people in eight developed nations indicated that women are more likely to take COVID-19 seriously and agree to comply with public safety measures.

GENETIC VULNERABILITY

Other genes besides those on the sex chromosomes might influence vulnerability to COVID-19. Andrea Ganna and Mark Daly, both at the University of Helsinki's Institute of Molecular Medicine Finland, have organized a global consortium called the COVID-19 Host Genetics Initiative to search for genetic variations that might put people at a higher or lower risk of becoming seriously ill. (Most variants affect the genes in subtle ways without interfering with their main functions.) Some of the more intriguing findings so far come from a study of 1,980 patients in Italy and Spain that was published in the *New England Journal of Medicine*. The researchers identified a cluster of variants on chromosome 3 that are associated with severe illness and respiratory failure in COVID-19 patients. A few of the genes encode key immune system molecules called cytokines. An additional one codes for a protein that interacts with the molecular doorway that the virus uses to enter cells: a surface enzyme called angiotensin-converting enzyme 2, or ACE2.

"Racism puts you at higher risk through the two mechanisms of being more infected because we are more exposed and less protected, and then, once infected, we are more likely to have a very severe course and die."
—Camara Phyllis Jones

More tentatively, the investigators found that genes on chromosome 9 that determine blood type could be linked to risk, putting people with type A blood in slightly greater danger of severe illness. "The jury is still out" on that finding, Ganna says, because a larger analysis did not confirm it. "But the signal on chromosome 3 is real and has been replicated robustly. It is associated with COVID severity."

A second genetics initiative, led by Jean-Laurent Casanova of the Rockefeller University and Helen Su of the National Institute of Allergy and Infectious Diseases, is searching for genes that might help account for two types of pandemic outliers. The first group is made up of young, otherwise healthy individuals who develop severe COVID-19, or, as Casanova puts it, "the guy who runs a marathon in 2019 and then he is in the I.C.U., intubated." The second group comprises people who remain uninfected despite extreme exposure, such as the virus-negative spouse of an ill patient. "We will test the hypothesis that some of them carry single-gene variations that make them naturally resistant to the entry of the virus," Casanova says. Such a gene, if it exists, would be analogous to one discovered in 1996 called *CCR5* delta 32, which confers resistance to HIV.

The identification of genes providing immunity or raising vulnerability, even if their effects are small, could offer useful clues for developing drugs for COVID-19, Ganna and Casanova say.

HOW UNDERLYING DISORDERS RAISE RISKS

From the earliest days of the pandemic, it has been clear that patients with certain chronic diseases are especially endangered by SARS-CoV-2. The *JAMA* report on 5,700 patients who were hospitalized for COVID-19 in and around New York City found that 94 percent had at least one chronic condition and 88 percent had more than one.

In mid-June the U.S. Centers for Disease Control and Prevention published an analysis of 287,320 confirmed cases for which accompanying conditions were reported. It showed that the most common ones were cardiovascular disease (in 32 percent of patients), diabetes (30 percent) and chronic lung disease (18 percent). People with COVID-19 who had chronic ailments such as these were six times as likely to be hospitalized and 12 times as likely to die as those who did not have them.

The high-risk conditions share a couple of things. First, most are associated with chronic low-grade inflammation, which compromises immune system function. Although the precise mechanisms by which inflammation does so are unclear, there are several leading suspects. One of them, at least in people who are significantly overweight,

is the activity of fat cells, which churn out a variety of inflammatory substances such as interleukin-6. "People with excess fat tissue may have a dysregulated immune response and not be able to counterbalance a severe infection," says Erin D. Michos, a cardiologist and epidemiologist at the Johns Hopkins University School of Medicine.

Diabetes, hypertension, cardiovascular disease and obesity have something else in common, Narasimhan observes: "All have upregulation of ACE2." Heightened expression of the protein in these conditions may possibly give the virus more entry points throughout the body. Doctors already know that SARS-CoV-2 breezes into a host via the respiratory tract and attacks the lungs. But additional evidence suggests that it may move into other ACE2-rich tissues such as the heart and kidneys. When it hits those organs, the damage—whether from the virus itself or the body's battle to contain it—can include blood clots and strokes, kidney injury, heart attacks, heart failure and arrhythmias.

Michos says that preexisting chronic conditions endanger COVID-19 patients in multiple ways. At the most elemental level, people with these ailments have less "cardiopulmonary reserve" to call on when the body is fighting a massive respiratory infection. Lack of oxygen from overwhelmed lungs forces the heart to work so hard that it can fail—especially if its capacity is already limited by narrowed arteries or heart disease. "It's like a tremendous stress test," Michos says. Another route to danger are the now infamous immune system freak-outs known as cytokine storms, which can further damage organs that are already fragile.

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—Camara Phyllis Jones

THE HAZARDS OF INEQUALITY AND RACISM

Beyond the inner layers, a wide range of external stressors also shape vulnerability to a virus such as SARS-CoV-2. As the pandemic has torn through the population of the U.S., it has taken an uneven toll. The CDC's mid-June analysis looked at 599,636 U.S. cases where race and ethnicity were reported. It found that 33 percent occurred in people of Latinx origin and 22 percent in Black people, even though these groups form, respectively, just 18 and 13 percent of the U.S. population. Some Native American groups, such as the Navajo, are also being hit tremendously hard. Mortality is disproportionate as well: Overall, Black Americans are dying at more than twice the rate of white people. In some states, their deaths occur at four or five times that rate.

Many factors contribute to this excessive toll, but they stem from the biased attitudes and actions of American society, not from Black American biology, says epidemiologist and family physician Camara Phyllis Jones of the Morehouse School of Medicine. "Race doesn't put you at higher risk. Racism puts you at higher risk," says Jones, who is a past president of the American Public Health Association. "Racism puts you at higher risk through the two mechanisms of being more infected because we are more exposed and less protected, and then, once infected, we are more likely to have a very severe course and die."

The higher risk of catching the virus comes both on the job and at home. An analysis conducted for Bloomberg found, for example, that only 19.7 percent of Black workers were in a position to work remotely during lockdowns, as opposed to 29.9 percent of white workers. A larger proportion of the jobs held by people of color are essential but low-paid ones. These are positions such as home health aide, grocery store worker, meatpacker, delivery worker and hospital orderly—roles that require constant contact with the public or crowded conditions with co-workers, both of which lead to high exposure to the coronavirus. The jobs do not come with the protections, such as telecommuting, afforded to those in higher-paid positions. For such workers, Jones says, "the personal protective equipment has been very slow in coming."

On top of that, she says, many people of color live in high-density, lower-income neighborhoods. "You're in a one-bedroom apartment with five people living there, and one is your grandmother," Jones relates. "You can't safely isolate, so people are more exposed by family members who are frontline workers that have gone out and then bring the infection home." In addition, compared with white Americans, a higher proportion of minority group members are held in prisons and sleep in homeless shelters, where infections spread quickly.

When people of color get the coronavirus, they are more at risk of becoming severely ill because they shoulder a greater burden of the chronic illnesses that can make COVID-19 more deadly. Black Americans, for example, suffer a 40 percent higher rate of hypertension and a 60 percent higher rate of diabetes than white Ameri-

cans. Native Americans, meanwhile, are twice as likely to have diabetes as white Americans. Structural inequities—such as neighborhoods that lack high-quality food options, the absence of safe places and leisure time to exercise, and poor air quality—contribute to these elevated levels of illness, noted Sherita Hill Golden, an endocrinologist at Johns Hopkins Medicine, at a May seminar on racial disparities and COVID-19.

Poorer access to medical care and discrimination within the health-care system add to these burdens. As the pandemic got worse in early spring, many people of color had a hard time getting tested for COVID-19. "Testing sites were often located in more affluent neighborhoods," Jones says. "Or there was drive-through testing. And what if you don't have a car?"

Golden points out that fear of immigration authorities and concerns about the Trump administration's new public charge rule—which makes it difficult for people who use Medicaid to gain legal immigration status—might be leading undocumented individuals to "avoid using [health] services they might otherwise have used."

Epidemiologists who study health inequities have found that lifelong stressors related to racial and ethnic discrimination take a direct toll on health. Ongoing elevated levels of stress hormones, such as cortisol and catecholamines, are thought to mediate this wear and tear and aggravate tissue damage. As a result, Black Americans tend to develop hypertension, glaucoma and some other aging-associated disorders earlier than white people do. The phenomenon has been termed "weathering" by Arline Geronimus, a professor of public health at the University of Michigan. Her research indicates that this premature aging cannot be explained by poverty and posits that it is the direct result of race-based injustice and bias.

As these and other COVID-19 risk factors become clearer, physicians and scientists say, health authorities need to shift resources and intensify protections for communities, groups and individuals who are most vulnerable. That effort has begun to happen in nursing homes, for example—though only after tremendous losses of life. Diagnostic testing for the virus is one such resource. "We know that there are communities at higher risk, and we need to be doing more testing there," Jones says. And that means examining people without symptoms who are able to spread the virus without knowing they are infected. "If we restrict ourselves to only testing people who are symptomatic," she warns, "we will just be documenting the course of the pandemic, but we will lose the opportunity to change the course of the pandemic."

On an individual level, people need to take stock of every layer of their own vulnerability, from the biological to the societal, and do what they can to mitigate hazards through pandemic-specific practices such as social distancing, mask wearing and avoiding crowds. (It is also important to try to maintain healthy habits, such as a good diet and regular exercise, although current circumstance can make doing so difficult.) At the same time, it is wise to remember that risk-group analyses reflect averages. An individual might have no obvious risk factors and still wind up desperately sick or dead. "The only job of this virus is to replicate itself," Jones points out. "It will make its way through all the susceptibles that it can find."

The Antibiotic Gamble

Paratek Pharmaceuticals made a lifesaving drug and got it approved. So why is the company's long-term survival still in question?

By Maryn McKenna

MICHELE SPATARI *GETTY IMAGES*

Maryn McKenna is a journalist specializing in public health, global health and food policy and a senior fellow of the Center for the Study of Human Health at Emory University. She is author most recently of *Big Chicken: The Incredible Story of How Antibiotics Created Modern Agriculture and Changed the Way the World Eats* (National Geographic Books, 2017).

AS THE COVID-19 PANDEMIC CAUGHT HOLD EARLY THIS YEAR, A SMALL DRUG COMPANY OUTSIDE Philadelphia was struggling to market a compound that could help patients battling for their lives.

Paratek Pharmaceuticals had spent more than 20 years developing and testing an antibiotic named omadacycline (Nuzyra), which went on sale in the U.S. in 2019 for use against bacterial infections. Although antibiotics can't fight the virus that causes COVID-19, almost 15 percent of people hospitalized with the disease go on to develop bacterial pneumonias, some of which are resistant to existing antibiotics.

Before COVID-19, antibiotic resistance was estimated to kill at least 700,000 people every year worldwide. That number could now climb as more people with the viral disease receive antibiotics to treat secondary infections or to prevent infections that come from being on a ventilator. That's where a drug such as omadacycline might help—if it can be delivered to people in time to save lives.

"COVID is a wake-up call," says Evan Loh, chief executive of Paratek, which has offices in Pennsylvania and Boston. Diagnostics, antibodies and vaccines are all key to preparing for a pandemic, he says, and "we need antibiotics, to give people the best chance of surviving this particular infection." But drugmakers who produce antibiotics face unique challenges.

In a bitter paradox, antibiotics fueled the growth of the 20th century's most profitable pharmaceutical companies and are one of society's most desperately needed classes of drug. Yet the market for them is broken. For almost two decades the large corporations that once dominated antibiotic discovery have been fleeing the business, saying that the prices they can charge for these life-saving medicines are too low to support the cost of developing them. Most of the companies now working on antibiotics are small biotechnology firms, many of them running on credit, and many are failing.

In just the past two years four such companies declared bankruptcy or put themselves up for sale, despite having survived the perilous, decade-long process of development and testing to get a new drug approved. When they collapsed, Achaogen, Aradigm, Melinta Therapeutics and Tetraphase Pharmaceuticals took out of circulation—or sharply reduced the availability of—five of the 15 antibiotics approved by the U.S. Food and Drug Administration since 2010.

Paratek has so far avoided the riptide that pulled so many others down, through a combination of conservative spending, experience and good fortune, including a lucrative government contract awarded late last year. But omadacycline's earnings, though steady, have not yet ensured Paratek's long-term survival.

"At the end of the day, Paratek is still going to have to sell a drug," says David Shlaes, a former pharmaceutical executive who is now an antibiotic-development consultant and author. "And it's not at all clear it's going to be able to sell as much as it needs to sell to make a profit."

COSTLY BUSINESS

Bringing a new antibiotic to market represents a Herculean feat. Only about 14 percent of antibiotics and biologicals in phase I trials are likely to win approval, according to the World Health Organization. A team of economists estimated in 2016 that the cost of getting from first recognition of an active drug molecule to FDA approval in the U.S. was $1.4 billion, with millions more required for marketing and surveillance after approval. When companies such as Eli Lilly or Merck made antibiotics in the mid-20th century, those costs could be spread across their many divisions. And when, as used to happen, big companies bought smaller ones whose new drugs showed preclinical promise, the purchase price covered any debt the small companies had incurred.

Those business models no longer exist. The trio that runs Paratek knows this because all three are big-company veterans. Loh worked at Wyeth Pharmaceuticals in Philadelphia with Adam Woodrow, Paratek's president and chief commercial officer, and with Randy Brenner, chief development and regulatory officer, on the successful antibiotic tigecycline (Tygacil), which was approved in 2005. (Wyeth sold its antibiotic portfolio to Pfizer in 2009.)

“When you come from a big company to a small company, your focus becomes: ‘How do I make sure this company survives?’” says Brenner, who previously also worked at Pfizer in New York City and at Shire in Lexington, Mass., now a subsidiary of Takeda Pharmaceutical Company in Tokyo. “Bigger companies don’t need to think like that. No matter what happens to a product, the company survives.”

Tigecycline is based on tetracyclines, one of the earliest classes of antibiotic; they were first used in 1948, just six years after penicillin’s debut. Over the years successive generations of tetracyclines arrived on the market and were undermined by resistance. Tigecycline’s structure incorporates tweaks that let it avoid those resistance mechanisms, but this comes at a cost: the drug can only be given intravenously.

This was a limitation. An intravenous drug would usually be given in hospitals and medical centers, making it both more expensive and less accessible to patients. So, as tigecycline was being developed, physician-researcher Stuart Levy—one of the giants of U.S. antibiotic-resistance research, based at Tufts University—proposed formulating yet another tetracycline relative that could also be delivered in pill form. With that goal in mind, he co-founded Paratek in 1996 with Walter Gilbert, a molecular biologist at Harvard University, who had won a share of the 1980 Nobel Prize in Chemistry.

In its early years Paratek formed partnerships with larger companies—German company Bayer, then Merck, then Novartis in Basel, Switzerland. But each deal dissolved as the corporations shifted focus or regulatory changes made omadacycline a bad financial bet. By 2012, when Loh was recruited, Paratek had accomplished phase I and II clinical trials of its compound and had amassed abundant data on its safety—but it was running out of money. Loh cut the staff from about 34 to six, closing the research laboratory while the executive team scrounged for funds. For nine months they went without salaries.

Evan Loh, chief executive of the U.S. firm Paratek Pharmaceuticals, leads a team that is striving to secure the future of a new antibiotic.

“I had an insolvency attorney on retainer for 18 months,” he recalls. “I talked to him every week. Should I open the doors on Monday? Did I have enough cash to do that?” In 2014 Paratek went public in a maneuver called a reverse merger, folding itself into a U.S. company named Transcept Pharmaceuticals that was already listed on the NASDAQ stock exchange but that had seen disappointing sales and was running with a skeleton crew. The deal earned Paratek $110 million, enabling it to launch omadacycline’s phase III trials and begin a careful restaffing program. In October 2018 the FDA approved the drug in oral and intravenous formulations against two conditions: complicated skin infections and community-acquired bacterial pneumonia. The 22-year journey was over—but the landscape into which omadacycline would launch was nonetheless still hazardous.

Loh, a cardiologist who had led transplant programs at two academic medical centers before turning to the pharmaceutical industry, knew that the drug was needed. But he was aware it would not be easy. “There’s nothing that happens in a hospital that can be successful if you don’t have an antibiotic,” he says. “You can’t have surgeries. You can’t have transplants. You can’t do anything. We have a product that we believe saves lives. Until we can make that successful for the long term, our mission is not done.”

LIMITED LIFE SPAN

Antibiotics present an enduring economic puzzle. These drugs changed the world. Yet despite their unique power,

HANNAH YOON *FOR NATURE*

the free market doesn't value them. The reasons are complex. Start with the obvious: antibiotics kill bacteria, living things that are constantly adapting to threats against their survival. As soon as a new compound is used, pathogens start evolving strategies to foil the attack. That means an antibiotic's useful life, and thus its earning potential, can be limited—a situation that doesn't occur for most other drugs.

The duration of a new antibiotic's life span wouldn't be that important if a company could sell a lot of it quickly, but both structural and ethical barriers work against that. Take the structural ones first. Relatively few patients have resistant infections that need treatment with new antibiotics, whereas most other drug categories are used to treat large numbers of people. The U.S. Centers for Disease Control and Prevention estimates that there are 2.8 million resistant infections annually in the U.S. For comparison, 7.4 million people in the U.S. take insulin to treat diabetes on a daily basis.

By one estimate, a new antibiotic needs to make at least $300 million in annual revenue to be sustainable. Other researchers estimate that the entire U.S. market for new antibiotics that work against carbapenem-resistant Enterobacteriaceae—one of the most resistant and most stubborn classes of infection—is $289 million a year. In other words, "there's room in this marketplace for maybe one drug," Shlaes says. "There's not room for more than one drug if people want a return on their investment."

Only a few of the companies now making antibiotics earn $100 million or more a year from them, according to analyses by the investment firm Needham in New York City. Most of the rest hover between $15 million and $50 million a year.

Then there are the ethical quandaries. Because any exposure of bacteria to an antibiotic risks the development of resistance, using that drug to treat one patient risks diluting its power to save others in the future. Thus, rules observed across health care, broadly called antibiotic stewardship, call for new antibiotics to be deployed slowly. That protects their reliability in the long term but ruins their sales. For instance, in 2018 three new antibiotics—including the one made by recently bankrupt Achaogen—were used in only 35 percent of cases that would have qualified for them. That was a win for stewardship, perhaps. It was a literal loss for the companies whose drugs would otherwise have been used.

John Rex, a physician and longtime drug developer who is chief medical officer at the antifungals company F2G in Manchester, U.K., and Vienna, sums up the paradox in this way: "Invent a bad antibiotic, and no one will use it. Invent a really good antibiotic, and really no one will use it."

INTO THE ABYSS

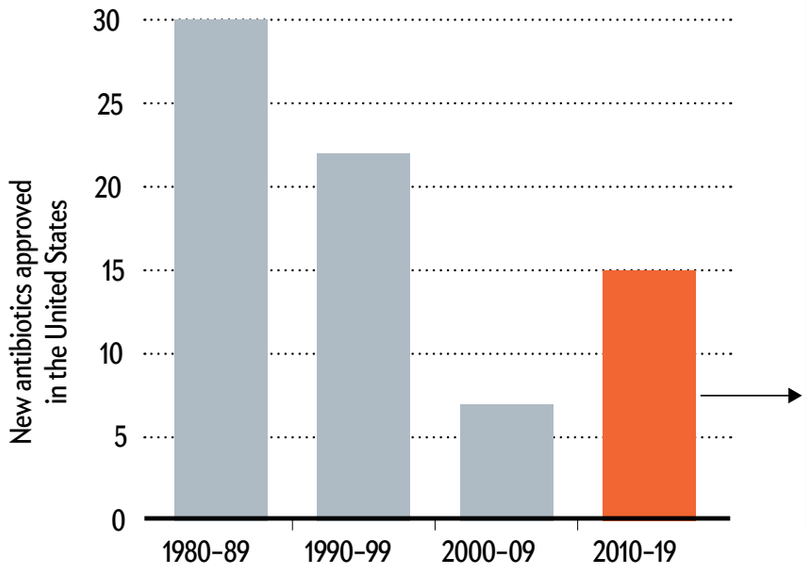
The 100-person team that makes up Paratek approached the end of 2019 in an unsettled mood. They were staring into what Woodrow calls "the abyss of commercialization: this three-year period where you spend a tremendous amount of money before you get any traction in terms of real sales." The antibiotic was selling steadily but slowly—it was on track to earn $13 million that year. Meanwhile Woodrow, Loh and Brenner had committed to doing postapproval studies and surveillance that they estimated would cost $70 million. And they had lost a guiding light: Levy, their co-founder, died in September 2019.

Then Christmas came early. The Biomedical Advanced Research and Development Authority (BARDA), a U.S. federal agency, awarded Paratek a five-year, $285-million contract to procure omadacycline for frontline troops who might be exposed to the bioweapon anthrax. (The purchase validated Levy's early insight on the value of an oral drug: endangered troops could pop the pills and move on rather than be tied to intravenous drips.)

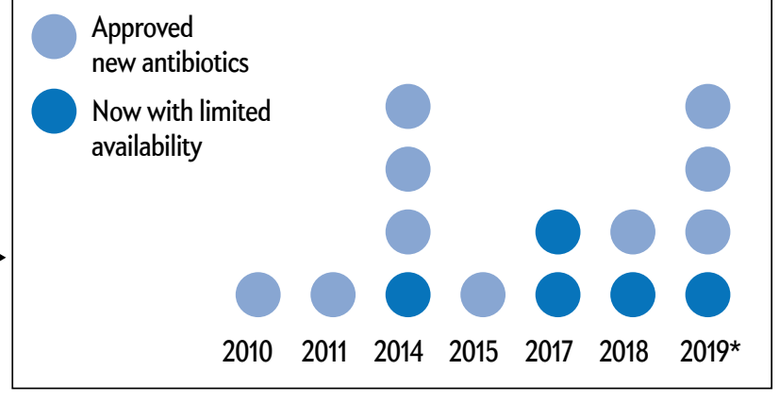
On receiving the news, Loh felt like he could finally

Trimming a Thinning Herd

Over the past several decades, the number of new antibotics approved for use in the U.S. has been declining, as it has elsewhere in the world.



Of the 15 new antibiotics that earned U.S. Food and Drug Administratin approval in the past decade, five have been essentially shelved as the companies that created them filed for bankruptcy or were sold off.



*No data for 2012, 2013 or 2016.

NATURE; SOURCES: "THE ANTIBIOTIC RESISTANCE CRISIS," PART 1: "CAUSES AND THREATS" BY C. LEE VENTOLA, IN *PHARMACY AND THERAPEUTICS*, VOL. 40; APRIL 2015; AXIOS

exhale. “This is a massive number—a gift,” he said not long afterward. “It gives us time to gain traction.”

The BARDA money acted like a bridge across the chasms that other companies had fallen into. In a small way, it also demonstrated the potential of incentives for repairing the antibiotic market, which policy makers in the U.S. and Europe have been debating for several years. There are two types, referred to as push and pull. “Pushes” propel new drug candidates from small companies through clinical trials and past approval. “Pulls” aim to ease the financial crunch after approval, when companies must promote their drug without violating antibiotic stewardship.

Push incentives have had some success. The nonprofit organization CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), based at Boston University, has gathered about $500 million in funding from U.S., U.K. and other European governments and philanthropies and is distributing the money to small companies. Since CARB-X was founded in 2016, it has given 67 companies about $250 million to support promising preclinical and phase I research.

BARDA—which is funding the separate search for coronavirus vaccines and therapeutics—also gives push grants that support companies doing the later clinical trials that bring drugs to approval. BARDA’s contract with Paratek was different, however. It was effectively a pull incentive, an infusion of cash arriving after omadacycline had been approved, at a point when postapproval surveillance and studies to support use of the drug for other infections would eat up slender earnings.

Other forms of pull incentive have been proposed by analysts and lawmakers, among others, and considered by the U.S. Congress, but they are much more controversial. These range from granting pharma companies extra time before other drugs they own become generic, called extended market exclusivity, to giving companies market-entry rewards of billions of dollars that release them from the need to push sales of their drug, which would otherwise accelerate the development of resistance. Yet another proposed pull incentive—which would raise the reimbursements paid to hospitals by the U.S. government for new antibiotics—was briefly added to the $2-trillion U.S. stimulus bill written in response to the coronavirus pandemic. The incentive was taken out again before the bill became law.

Many antibiotics are in short supply as a side effect of the coronavirus pandemic.

SIMON DAWSON *GETTY IMAGES*

No one has yet found a path past political reality: in the eyes of many voters and politicians, pharma companies are opportunists, inflating U.S. drug prices to unconscionable heights. There were multiple congressional hearings on drug prices in 2019 alone, and in July, President Donald Trump signed several executive orders aimed at forcing prices down. Making things easier for any drug company, even a small one producing a much needed antibiotic, faces strong political resistance.

Alan Carr, a molecular biochemist and senior analyst at Needham, says there is not yet a clear path to what works to support antibiotic research—not for incentives and not for investors, either. “What has complicated things for investors is that there is a need for new antibiotics—but not in every space within antibiotics,” he says. “There are certain infections where there’s a real unmet need where we don’t have any antibiotics. And then there are other areas where we have plenty. Unfortunately, what has happened is that investors have

lumped the whole space together. So they want nothing to do with any of them."

PANDEMIC CURVEBALL

The BARDA contract turned Paratek from a company with less than a year's worth of cash in the bank to one that could count on funding to the end of 2023. That guaranteed its immediate future, although it did nothing to solve the long-term problem of needing to earn more from the drug than the market seemed willing to pay. And then the coronavirus hit.

When cases of SARS-CoV-2 started increasing in the U.S., Loh and his team were unnerved. The Paratek sales force had been doing the normal rounds, explaining omadacycline to infectious disease specialists and hospital pharmacists, hoping to have it picked up by the formulary committees that govern which medications hospitals routinely keep to hand. Its work was paying off. Month after month sales of omadacycline were rising by more than 10 percent. When the lockdowns started, all of those meetings ended. The company worried its sales would stall as well. But in monthly data gathered since the epidemic began, the steady increase has continued.

"New prescribers, in a lockdown period—I expected that to go to zero," says Christine Coyne, Paratek's vice president of marketing. "But we are still seeing double-digit growth."

It is too soon to say what drives those sales. Enough case reports have now been published for researchers to feel confident that bacterial pneumonia is a complication of COVID-19 in 15 to 20 percent of patients. And in parts of the U.S., the most common cause of bacterial pneumonia (*Streptococcus pneumoniae*) is resistant to azithromycin, the most common generic antibiotic, in up to 50 percent of cases. That could drive adoption of a new drug for which resistance has not been recorded. Other publications confirm that significant amounts of antibiotics are being prescribed to people with COVID-19 who are on ventilators, even when pneumonia has not been diagnosed. This is an insurance policy against patients getting hospital-acquired infections and because, in the absence of enough personal protective equipment, the procedures needed to confirm bacterial pneumonia are too risky for staff to undertake.

As a side effect of the pandemic, many other antibiotics are in short supply. That's a result of both interruptions in international trade—the active ingredients of most antibiotics come from China—and domestic influence. For instance, after Trump announced his support in March for the unproven and now largely discredited combination of hydroxychloroquine and azithromycin, several manufacturers of azithromycin announced that panic buying had triggered shortages.

If those events are boosting sales, that is to Paratek's benefit. They also underline the good fortune of the BARDA contract coming when it did. The company's supply chain avoids China and is based entirely in Europe. And as a condition of protecting national defense, a clause in the BARDA contract requires the company to build a parallel supply chain fully within the U.S. to avoid disruptions from any future outbreaks.

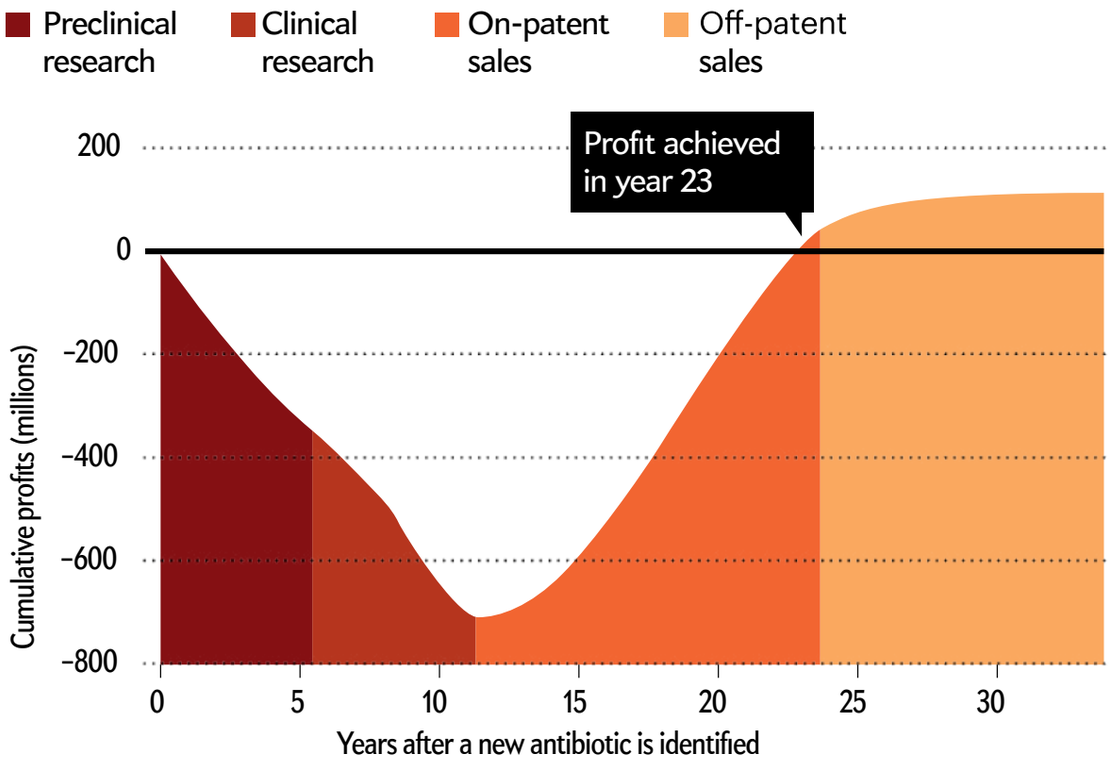
To the Paratek team, omadacycline's applicability to this ongoing crisis is validation of the company's commitment to stick with a product that it believed was needed. Equally, it has demonstrated how important it is to anticipate emergencies, and to provide for crucial medical interventions before one begins. The U.S. failed to do that for masks, respirators and other equipment that protects health-care workers from infection. It almost failed to do that for the provision of antibiotics, too.

"Coronavirus ought to say to the public, 'If you don't have technology on the shelf when something like this happens, you can't wait a year or two—or even three or five—in order to get it there,'" Loh says. "You can't be at the bedside and say to a company: 'Can you make this for me today?'"

This article is repoduced with permission and was first published in Nature *on August 19, 2020.*

Long Path to Profitability

Estimates suggest that it takes more than 20 years to see any profit from a newly developed antibiotic. Once a drug goes off patent, increasing that profit becomes much more difficult.



NATURE; SOURCE: *SECURING NEW DRUGS FOR FUTURE GENERATIONS: THE PIPELINE OF MEDICATIONS.* THE REVIEW ON ANTIMICROBIAL RESISTANCE, MAY 2015

Who Will Get a COVID-19 Vaccine First? Access Plans Are Taking Shape

Advisory groups around the world have released guidance to prioritize health-care workers and those in frontline jobs

By Nidhi Subbaraman

A nurse prepares to inoculate a volunteer with Russia's new coronavirus vaccine in a postregistration trial at a clinic in Moscow on September 10, 2020.

NATALIA KOLESKIKOVA *GETTY IMAGES*

Nidhi Subbaraman is a science writer based in Washington, D.C.

WHETHER IT TAKES WEEKS, AS U.S. PRESIDENT DONALD TRUMP HAS HINTED, OR MONTHS, as most health-care experts expect, an approved vaccine against the coronavirus is coming, and it's hotly anticipated. Still, it will initially be in short supply while manufacturers scale up production. As the pandemic continues to put millions at risk daily, including health-care workers, older people and those with pre-existing diseases, who should get vaccinated first?

A strategic advisory group at the World Health Organization (WHO) weighed in with preliminary guidance for global vaccine allocation, identifying groups that should be prioritized. These recommendations join a draft plan from a panel assembled by the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM), released in September.

Experts praise both plans for addressing the historic scale and unique epidemiology of the coronavirus pandemic. And they commend the NASEM for including in their guidance minority racial and ethnic groups—which COVID-19 has hit hard—by addressing the socio-economic factors that put them at risk. The WHO plan, on the other hand, is still at an early stage and will need more detail before its recommendations can become actionable, others say.

"It's important to have different groups thinking through the problem," says Eric Toner, an emergency-medicine physician and pandemics expert who has done similar planning at the Johns Hopkins Center for Health Security in Baltimore. And although the plans differ somewhat, Toner says that he sees a lot of agreement. "It's great that there's a consensus of opinion on these issues."

HEAD OF THE LINE

The WHO's guidance at this point lists only which groups of people should have priority access to vaccines. The NASEM guidance goes a step further by ranking priority groups in order of who should get a vaccine first.

After health-care workers, medically vulnerable groups should be among the first to receive a vaccine, according to the NASEM draft plan. These include older people living in crowded settings and individuals with multiple existing conditions, such as serious heart disease or diabetes, that put them at risk for more serious COVID-19 infection.

The plan prioritizes workers in essential industries, such as public transit, because their jobs place them in contact with many people. Similarly, those who live in certain crowded settings—homeless shelters and prisons, for example—are called out as deserving early access.

Many nations already have general vaccine-allocation plans, but they are tailored for an influenza pandemic rather than the new coronavirus. They typically prioritize children and pregnant women; the COVID-19 plans do not, however, because most vaccine trials currently do not include pregnant women, and the coronavirus seems to be less deadly to children than influenza is. The NASEM guidance, in fact, recommends giving children COVID-19 vaccines during one of the final phases of its allocation plan.

Unlike the NASEM guidance, the WHO plan notes that government leaders should have early access, but it cautions that people prioritized in this way should be "narrowly interpreted to include a very small number of individuals."

"We were very concerned about the possibility that this group could serve as a loophole through which a truckload of people who identify as important could then push themselves to the front of the line," says Ruth Faden, a bioethicist at the Johns Hopkins Berman Institute of Bioethics, who was part of the group that drafted the WHO guidance.

HARD-HIT GROUPS

Access for disadvantaged groups is addressed in both the plans. Looking to past failures, the WHO guidance urges richer countries to ensure that poorer countries receive vaccines in the earliest days of allocation. During the 2009 H1N1 flu pandemic, "by the time the world had gotten around to figuring out how to get vaccines to some

low- and middle-income countries, the pandemic was over," Faden says.

But the WHO proposal does not yet suggest how nations might resolve the tension between allocating vaccines in a country versus allocating them among countries, says Angus Dawson, a bioethicist at the University of Sydney in Australia, who published a review of national pandemic allocation ethics earlier this year. In other words, should harder-hit nations receive a bigger allocation of an early vaccine before other nations have a chance to dose their high-priority groups?

The NASEM was asked to develop its allocation plan by both the U.S. Centers for Disease Control and Prevention, which will set the U.S. government's COVID-19 vaccination plan, and the U.S. National Institutes of Health, which is coordinating vaccine and treatment trials. When tapping NASEM to create the proposal, leaders from both agencies requested that the report address how to give vaccine priority to "populations at high risk," including "racial and ethnic groups" that have been affected by COVID-19 and have died at disproportionately higher rates than have other groups in the U.S. The panel determined that these groups are vulnerable chiefly for socioeconomic reasons tied to systemic racism—for example, they have high-risk jobs and live in high-risk areas—and therefore addressed the request through this lens, without singling out the groups because of their racial or ethnic identities.

"We really are trying to make sure that people of color, who have been disproportionately impacted, will also have priority—but for the factors that put them at risk, not highlighting just their racial and ethnic makeup," says Helene Gayle, president and chief executive officer of the Chicago Community Trust and a co-chair of the NASEM committee that drafted the proposal.

Faden says the recommendations acknowledge the current focus on racial injustice in the U.S. "I was reading to see: Does this report speak to the cultural moment in the U.S.? Does it speak to racism and other forms of structural inequality? And it does," she says.

"We really are trying to make sure that people of color, who have been disproportionately impacted, will also have priority—but for the factors that put them at risk, not highlighting just their racial and ethnic makeup."

—Helene Gayle

The NASEM panel therefore proposes a lengthy list of essential workers who should get priority access to a vaccine, including grocery-store workers, transit workers and postal workers. People from hard-hit ethnic and racial groups are overrepresented in these jobs.

U.S. states should also use the CDC's Social Vulnerability Index to help to make decisions about allocation, the NASEM plan suggests. A geography-based tool that typically guides the allotment of aid after a national disaster, it accounts for where people live, as well as health conditions that are overrepresented in Black and Indigenous individuals and other people of color.

HEEDING THE ADVICE

The WHO's strategic advisory group will continue to update its guidance, first to assign rankings to its priority groups and then to include real data from vaccine trials, such as how effective a given vaccine is in older people. Although the guidance is available to all WHO member nations, none is compelled to implement it.

In the U.S., at the beginning of October the NASEM committee released its final plan for a four-phased vaccine distribution plan. Ultimately the CDC will consider these recommendations among others while developing its own vaccine-allocation plan for the country, expected later in 2020.

That will be the guidance that public health departments, doctors and pharmacies throughout the U.S. should follow when handing out vaccines—assuming that one has been proven safe and people are willing to take it.

In the lead up to the U.S. presidential election, Trump had been rooting for a vaccine to be ready by November. But a perception that the vaccine has been rushed could erode people's trust in it, says Sandra Crouse Quinn, a behavioral scientist at the Center for Health Equity at the University of Maryland, College Park. This could make vaccine-allocation plans less effective.

When it comes to putting any of these plans into action, Dawson says, "You have to take into account the political context."

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Fast Coronavirus Tests

What They Can and Can't Do

Health-care workers test a resident of Mumbai, India, for coronavirus infection using a rapid antigen assay.

Rapid antigen tests are designed to tell in a few minutes whether someone is infectious. Will they be game changers?

By Giorgia Guglielmi

ANSHUMAN POYREKAR *GETTY IMAGES*

Giorgia Guglielmi is a freelance science journalist in Basel, Switzerland.

THE U.S. LEADS THE WORLD IN COVID-19 DEATHS BUT LAGS behind many countries—both large and small—in testing capacity. That could soon change.

At the end of August the U.S. Food and Drug Administration granted emergency-use approval to a new credit-card-sized testing device for the coronavirus that costs $5, gives results in 15 minutes and doesn't require a laboratory or a machine for processing. The U.S. is spending $760 million on 150 million of these tests from health-care company Abbott Laboratories, headquartered in Abbott Park, Ill., which plans to ramp up production to 50 million per month in October.

The tests detect specific proteins—known as antigens—on the surface of the virus and can identify people who are at the peak of infection, when virus levels in the body are likely to be high. Proponents argue that this could be a game changer. Antigen tests could help to keep the pandemic at bay because they can be rolled out in vast numbers and can spot those who are at greatest risk of spreading the disease. These tests are also a key element in the testing strategies of other countries, such as India and Italy.

Antigen assays are much faster and cheaper than the gold-standard tests that detect viral RNA using a technique called the polymerase chain reaction (PCR). But antigen tests aren't as sensitive as the PCR versions, which can pick up minuscule amounts of the SARS-CoV-2 virus that causes COVID-19.

This difference raises some concerns among specialists, who worry that antigen tests will miss infectious people and result in outbreaks in countries that have largely controlled coronavirus transmission. Others view the lower sensitivity as an attribute because some people who receive positive PCR test results are infected but are no longer able to spread the virus to others. So antigen tests could shift the focus to identifying the most infectious people.

At present, antigen tests are administered by trained professionals, but some companies are developing versions that are simple enough to be used at home—similar to pregnancy tests.

"Making the tests faster, cheaper, easier is definitely the goal—and I think the antigen test is the way to get there," says Martin Burke, a chemist at the University of Illinois at Urbana-Champaign, who is co-developing rapid tests, including antigen-based assays. "This is by no means the perfect solution, it's just the fastest thing we could get going now," he says.

WHAT TESTS ARE THERE, AND HOW DO THEY WORK?

Tests for COVID-19 fall into two categories: diagnostic tests such as PCR and antigen assays, which detect parts of the SARS-CoV-2 virus, and antibody tests that sense molecules that people produce when they have been infected by the virus. Antibodies can take several days to develop after an infection and often stay in the blood for weeks after recovery, so antibody tests have limited use in diagnosis.

The high-sensitivity PCR tests are almost 100 percent accurate in spotting infected people, when they are administered properly. But such tests generally require trained personnel, specific reagents and expensive machines that take hours to provide results.

Countries such as South Korea and New Zealand have succeeded in boosting PCR-based testing, but scaling up these tests has proved difficult elsewhere. The U.S., for example, has seen a slow and poorly coordinated response to outbreaks, faulty tests from the Centers for Disease Control and Prevention and problems with the supply chain. All of this has hindered efforts to collect and process samples for PCR, pushing waiting times to days or even weeks. These delays, along with a lack of tests, have contributed to the rampant spread of COVID-19 across the country, which by late October had seen more than 229,000 deaths from the disease.

A typical antigen test starts with a health-care professional swabbing the back of a person's nose or throat—although companies are developing kits that use saliva samples, which are easier and safer to collect than a swab. The sample is then mixed with a solution that breaks the virus open and frees specific viral proteins. The mix is added to a paper strip that contains an antibody tailored to bind to these proteins, if they are present in the solution. A positive test result can be detected either as a

fluorescent glow or as a dark band on the paper strip.

Antigen tests give results in less than 30 minutes, do not have to be processed in a lab and are cheap to produce. Yet that speed comes with a cost in sensitivity. Whereas a typical PCR test can detect a single molecule of RNA in a microliter of solution, antigen tests need a sample to contain thousands—probably tens of thousands—of virus particles per microliter to produce a positive result. So if a person has low amounts of virus in their body, the test might give a false negative result.

When used on people who were positive for SARS-CoV-2 in a standard PCR test, Abbott's antigen assay correctly spotted the virus in 95 to 100 percent of cases if the samples were collected within a week of the onset of symptoms. But that proportion dropped to 75 percent if samples were taken more than a week after people first showed symptoms. The sensitivity—or the rate of detecting infections correctly—of the other antigen tests used in the U.S. is between 84 and 98 percent if a person is tested in the week after showing symptoms.

Companies and academic research labs are also rolling out other tests that are faster, cheaper and more user-friendly than standard PCR assays, although they are not being produced on the same scale as antigen tests. Some of these other tests use the gene-editing tool CRISPR to zero in on genetic snippets of the coronavirus. Others are quicker variants of the PCR test that use different reagents, meaning they are not limited by the same supply-chain problems. Saliva-based PCR tests, for example, are being used as screening tools in universities and for professional basketball teams.

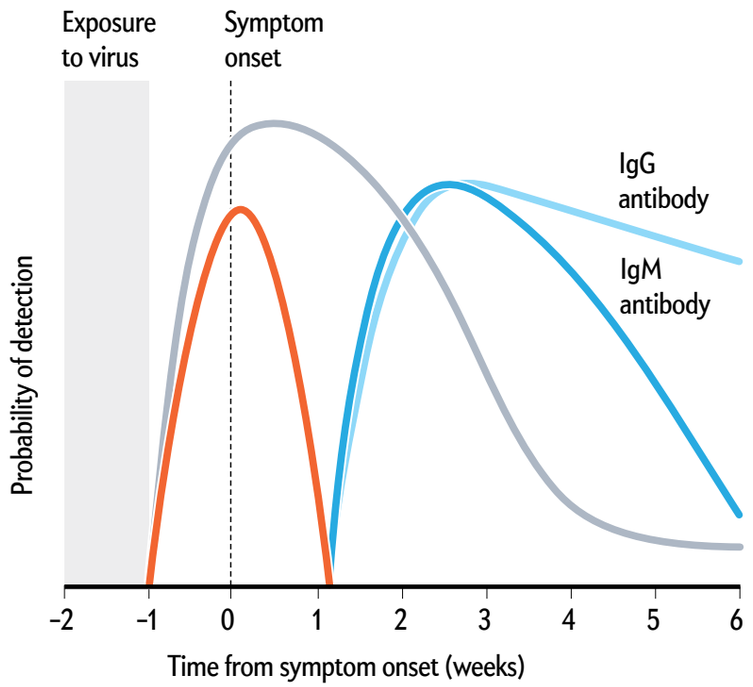
WHICH TESTS TELL WHETHER SOMEONE IS INFECTIOUS?

Although the PCR method can test whether someone is infectious, it also detects people who have the virus but are not likely to spread it.

Catching COVID-19

Different types of COVID-19 test can detect the presence of the SARS-CoV-2 virus or the body's response to infection. The probability of a positive result varies with each test before and after symptoms appear.

- **PCR-based tests** detect small amounts of viral genetic material, so a test can be positive long after a person stops being infectious.
- **Rapid antigen tests** detect the presence of viral proteins and can return positive results when a person is most infectious.
- **Antibody tests** detect the body's immune response to the virus and are not effective at the earliest phase of infection.



Antigen-based testing, in contrast, could help to rapidly identify people who have high levels of virus—those who are most likely to be infectious to others—and isolate them from the community, says Marion Koopmans, a virologist at the Erasmus University Medical Center in Rotterdam, the Netherlands. "The question is, What is the safe limit? Because the moment you get that wrong, the whole idea implodes," she says. It is still unclear what viral load is the threshold below which a person is no longer contagious, says Koopmans, who is working with the World Health Organization (WHO) to determine a standard to validate rapid tests. "It would be very worrying if everyone does that on their own, using different criteria," she says.

Viral load peaks early in SARS-CoV-2 infections and then gradually declines, with tiny amounts of virus RNA staying in someone's nose or throat for weeks or possibly months. And although there are not enough data to equate different viral levels with how infectious people are, there is evidence that individuals are unlikely to spread the virus about eight to 10 days after showing symptoms.

"If you're at risk of transmitting the virus to somebody else, you're going to have plenty of viral particles—those would certainly show up in antigen tests," says Michael Mina, an infectious disease immunologist at the Harvard T. H. Chan School of Public Health, who has been a vocal proponent of antigen tests.

There are challenges at the start of the infection, when people have low levels of the virus. The answer, Mina says, is frequent testing—done multiple times per week. This could quickly identify infected people, even if the assays are less sensitive than a PCR-based test because the amount of virus in their noses and throats rises within hours, he says.

Mina and his colleagues have used statistical models to assess this strategy. In a preprint updated on September 8, they suggest that testing people twice a week with a relatively insensitive test could be more effective at curbing the spread of SARS-CoV-2 than are more accurate tests done once every two weeks. Another study that modeled different scenarios for safely reopening university campuses reported similar findings.

To slow outbreaks, the focus should be on identifying

those who are at risk of spreading SARS-CoV-2 to other people rather than on spotting anyone who is infected with it, some experts say.

When used as a screening tool to frequently assess as many people as possible, rapid antigen tests could be "a game changer," says Rebecca Lee Smith, an epidemiologist at the University of Illinois.

HOW DO COUNTRIES PLAN TO USE ANTIGEN TESTS?

At the beginning of April, as coronavirus outbreaks raged across the world, India had tested only about 150,000 people—one of the lowest testing rates per capita worldwide. On August 21 the country conducted more than one million coronavirus tests in a single day. It reached that milestone after Indian authorities began using antigen assays to boost testing capacity.

Delhi was the first Indian state to begin using rapid antigen tests, in June. By mid-July the number of cases there had decreased, and the daily death counts had plateaued, suggesting that the tests might have played some part in controlling the spread of the virus. Epidemiologist K. Srinath Reddy, president of the Public Health Foundation of India, a nonprofit organization in New Delhi, says that the Delhi example is interesting but not clear-cut: he notes that the government started to lift lockdown restrictions in August, which led to a surge in infections. "Rapid antigen tests have picked up the increased number of cases, but whether they have been successful in limiting the spread of COVID, we'll only know in the next couple of months," Reddy says.

So far India has approved the use of three antigen tests for screening large numbers of people, whether or not they have symptoms. One of the kits was evaluated by the Indian Council of Medical Research (ICMR) and the All India Institute of Medical Sciences, which found that the test detected infections between 51 and 84 percent of the time. Guidance from the ICMR says that people who have a negative result from an antigen test should also get a PCR test if they show symptoms, to rule out the possibility that the rapid test missed an infection.

A technician in a mobile unit conducts rapid antigen tests for COVID-19 in New Delhi.

MAYANK MAKHIJA *GETTY IMAGES*

The WHO and the CDC have also advised getting a PCR test if people showing symptoms test negative with a rapid antigen test. The FDA has so far granted emergency-use authorization for four antigen tests, each of which has a higher sensitivity than those used in India. The 150 million tests bought from Abbott will be used in schools and "other special needs populations," according to the Department of Health and Human Services. The FDA, however, has authorized antigen-based tests only for people who have had symptoms for 12 days or fewer. Tests must be prescribed by a physician and administered by a health-care professional.

Other countries are also considering the use of rapid antigen tests to meet targets. In July the Philippine Society for Microbiology and Infectious Diseases issued temporary guidelines for clinicians and health-care workers, saying that antigen tests could be used as an alternative to PCR for diagnosing a coronavirus infection during the first week in people with symptoms. But it also recommends that all negative results should be confirmed with a PCR-based assay, says Edsel Salvaña, an infectious diseases expert at the University of the Philippines Manila, who is advising Philippine officials on rapid testing.

Antigen-based tests are being used in some of Italy's major airports to screen people who arrive from four

Mediterranean countries considered to have a high risk of infection. Negative results do not have to be confirmed with a PCR test. The Italian health minister, Roberto Speranza, has announced plans to use antigen tests to screen passengers at all of the country's airports, and a group of experts has urged the Italian government to use the rapid tests in schools and universities.

But others do not think rapid antigen tests are a good idea. When trying to contain small outbreaks, such as those happening in Italy, public health authorities should use assays that are highly accurate because missing even just one positive individual could lead to a steep increase in the total number of cases, says Andrea Crisanti, a microbiologist at the University of Padua.

Some researchers worry that there will not be enough antigen tests available to greatly expand their use. "Rapid tests right now are for the happy few," Koopmans says. "If we want to take these assays responsibly forward, we should talk about whether they can be produced to levels that would make them globally available."

COULD ANTIGEN ASSAYS BE USED AT HOME LIKE PREGNANCY TESTS?

Several experts have promoted the idea of developing an antigen test that is cheap and simple enough to use at home, without a health-care worker administering it.

Burke says what is needed is something as easy as a pregnancy test. "You just spit into a tube, put a piece of paper in it, and you get the result within minutes," he says. "Testing should become a part of life: in the morning you take your cereals, your vitamins, and you quickly check your status," he says.

A few companies are developing simple paper-strip antigen tests. But drug regulators have not yet approved them for emergency use. "We don't have a lot of real-life experience with these tests, and a lot of the validations have only been done in the laboratory," Salvaña says.

A testing center at the international airport in Rome. Italy plans to use rapid antigen tests to screen passengers at all of its airports.

Beyond concerns about costs and availability, researchers worry that, with an over-the-counter test, people who get positive results might not follow up with public health authorities, so their contacts will not be traced. Another risk would be people "gaming the system," Smith says—for example, getting someone else to take their test—so they can be sure of a negative result and avoid quarantine. Without incentives such as freely available tests and a living salary for those who have to isolate, testing and self-isolation could become a luxury reserved for wealthier people, others have argued.

Another concern is that people will get a false sense of security from tests that have only limited accuracy. "There's a big risk that the moment these tests become widely available, people will just use them and say, 'It's negative, so I'm clear,'" Koopmans says.

Even when testing negative, people should continue to wash their hands, wear masks and avoid gathering in big groups, she says. Testing, she adds, "cannot replace the basic control measures that need to be in place to keep this virus controlled."

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SIMONA GRANATI *GETTY IMAGES*

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POLICY & ETHICS

Medical Education Needs Rethinking

Under the lingering influence of the 110-year-old Flexner report, medical schools still minimize social and environmental factors in the understanding and treatment of disease

As COVID-19 infections and hospitalizations remain high across the country, our weakened public health system has never been more frustrating to frontline clinicians. While it's tempting to blame politicians, it's also insufficient. To understand why this pandemic has had such deleterious effects, we must examine why the study of diagnosis and treatment of disease separated itself from the study of preventing disease—or, more succinctly, why medicine and public health are considered apart from each other.

Tracing this unfortunate disconnect leads us to a cause from 110 years ago: the 1910 Flexner report.

In the early 1900s the length, focus and quality of medical training differed from school to school, resulting in significant variability from doctor to doctor. Spurred by this disarray, the American Medical Association commissioned the Carnegie Foundation to help reform medical education. Together they hired Abraham Flexner, founder of a successful prep school and the future founding director of the prestigious Institute for Advanced Study in Princeton, N.J., to assess the state of medical education. After visiting every medical school in North America, he produced the report.

Abraham Flexner in 1894.

GETTY IMAGES

The Flexner report—and the money tied to its implementation—is the medical education system we're familiar with today: competitive admission criteria, traditional pedagogy and the scientific method as its central tenets. The report established the individual biomedical model, which focuses exclusively on biological causes of disease, excluding any social and environmental factors, as the gold standard.

It also led to the disproportionate closing of historically Black medical colleges, contributing to physician workforce disparities that still exist today, and effectively cleaved the study of medicine from the study of public health.

Even more than a century later some modern medical academics cling to this paradigm. Former University of Pennsylvania medical school dean Stanley Goldfarb propelled this idea to prime time with a 2019 *Wall Street Journal* op-ed entitled "Take Two Aspirin and Call Me by My Pronouns," in which he refers to topics such as firearms violence, racial bias, health disparities and climate change as "progressive causes only tangentially related to treating illness" and not worthy of inclusion in the curriculum.

Goldfarb hasn't been the only one to echo the Flexner report. Thomas Huddle, professor of medicine at the University of Alabama, dismissed advocacy for societal good as out of scope in academia in a 2011 article in *Academic Medicine,* stating: "Although advocacy may coexist alongside the core university activities of research and education, insofar as it infects those activities, advocacy is likely to subvert them, as advocacy seeks change rather than knowledge."

But Goldfarb and Huddle and the people who agree with them are a minority in the medical community.

The American College of Physicians strongly rebutted Goldfarb's essay and directed detractors to its public health policy statements. In its recent position statement, the Society for General Internal Medicine calls for cross-cutting action to address the social determinants of health, declaring that "direct policy action will have the most far-reaching impact on improving health, equity, and well-being." The American Academy of Family Physicians lays out sweeping policy recommendations to promote health equity, and the American Academy of Pediatrics calls for comprehensive work to combat racism as "health equity is unachievable unless racism is addressed."

Even the American Medical Association's Principles of Medical Ethics require physicians to actively "support access to medical care for all people." The Physician's Charter recognizes the "primacy of patient welfare, patient autonomy and social justice."

Despite these bold calls to action and majority support, the Flexner report still has a grasp on medical education. To be fair, no one cites the Flexner report in defending the medical status quo, and the biopsychosocial model has supplanted the biomedical model in many settings.

But the Flexner report's legacy wears on in this "tradition of excellence" that minimizes social and environmental factors and, in doing so, undermines our understanding and treatment of disease.

For example, researchers often cite the individual attribute of race as a risk factor for disease without interrogating the associated environmental experience of racism. Similarly, the lens in medical education is often inclusive of poverty but not oppression, race but not racism, sex but not sexism, and homosexuality but not homophobia. We can see the biomedical model's influence in the field of psychiatry in the stark division of labor between the physician who assesses the patient's neurobiology and treats with prescription drugs and the therapist who assesses psychosocial factors and treats with therapy.

As long as the scientific method exclusively continues to dictate what physicians do, medicine will resist the responsibility to engage in upstream work to dismantle social causes of disease. Advocacy—defined by physician advocates as activities "promoting the role of science and evidenced-based medicine in the creation of health and social policy"—has been treated as if it's unscientific and therefore an unworthy endeavor, even though, through their various professional organizations' public policy positions, most physicians think it's just the opposite. While advocacy is taught in some training programs, it is not universal, and the curriculum is heterogeneous. Lack of mentorship, sponsorship and funding for advocacy in academic medicine poses significant challenges to incorporation of it into the physician career.

We're seeing similar conditions that led up to the commission of the Flexner report years ago. The purpose of the report was to standardize education so that doctors would be uniformly trained. Advocacy education, while popular, isn't standardized, at least not in the right way; most support it, but only some get it.

But the U.S. is now at a critical public health turning point, and advocacy in medicine can no longer be optional. The dual crises of COVID-19 and police brutality have captured our collective attention and exposed our considerable vulnerabilities. Current COVID-19 statistics show infection and mortality rates in the U.S. to be among the highest in the world; our daily infection rate in late October hit 100,000. Police brutality is a uniquely American problem; more than 1,000 people are killed by the police every year, whereas in other G7 nations such incidents are exceed-

ingly rare. Black and brown communities are disproportionately affected by both COVID-19 and police brutality, crystallizing racism as a fundamental public health problem in America.

The cracks in our nation's health exposed by COVID-19 demonstrate that we still need to evolve from these clearly outdated assumptions of yesteryear. Medicine as a discipline needs a strong public health foundation. The most effective public health strategies to combat COVID-19—universal masking, test/trace/isolate, and closures—have all been thwarted in the name of politics.

To begin to reintegrate medicine and public health, we must incorporate advocacy as a core competency across the educational spectrum: from medical school to residency to continuing medical education. Public health is not just for politicians. We must equip physicians with the necessary skills to effectively advocate for the policies we so desperately need to care for our patients.

The Flexner report needs to be supplanted by another document that stitches medicine and public health back together. A replacement for the Flexner report can catalyze concrete action and may provide cover and justification for those people who've met resistance while trying to incorporate advocacy into medical education and practice.

Even if it is only a symbolic gesture to indicate abandonment of outdated ways of thinking, the American Medical Association would be wise to commission another report to show that Flexner's thinking, while revolutionary for his time, isn't applicable anymore.

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BEHAVIOR & SOCIETY

We Must Reduce the Trauma of Medical Diagnoses

If a diagnosis is not delivered with care, it can form an intense "flashbulb memory"

THOMAS BARWICK *GETTY IMAGES*

At some point in your life, you will likely experience the anxiety of sitting in a hospital room, waiting for a serious medical diagnosis. Even those lucky enough to avoid that situation will likely accompany a loved one—a parent, grandparent or child—who is receiving the news. You might remember the stiffness of the chair, the pattern of the hospital gown or the doctor's folded hands. Whatever the diagnosis—cancer, Alzheimer's disease, diabetes or even COVID-19—the event is not one you will easily forget.

Powerful emotional experiences such as this one can develop into so-called flashbulb memories: recollections that are highly salient and appear as vivid as a snapshot. Most of us who lived through the assassination of President John F. Kennedy or 9/11 are confident we can pinpoint precisely where we were when we found out about the event. These memories are not perfect—they are distorted like any other recollection. Yet when they recount the experience, people describe it as if it happened yesterday. And these memories influence our personal identity, social bonds, decision-making and behaviors over time. After the 2013 Boston Marathon bombing, for example, those who witnessed acts of heroism and remembered them in detail were more likely to engage in helping behaviors such as donating blood or supporting Boston-related charities, even months after the attack.

In a recent study we demonstrated that for some individuals, a medical diagnosis event does create a flashbulb memory that endures for years after the fact. But our findings also showed that the intensity of these memories and the emotions associated with them depend on the doctor's delivery, which either softens the impact or prolongs the pain. Medical professionals would be wise to carefully consider how they convey such news.

For our study, we surveyed more than 300 mothers, recruited through support groups on social media, who had received a diagnosis of

Down syndrome for their child. The mothers ranged in age from 21 to 79 years and had been given the diagnosis between 52 years and one month ago. In the survey, they wrote a narrative describing in detail how they were informed their child had Down syndrome—incorporating as many specifics as they could about the day, location, weather, time and other features. These narratives were coded and rated using the Flashbulb Memory Checklist (FBMC) for specificity. The mothers also responded to a series of statements from the Autobiographical Memory Questionnaire (AMQ) to indicate the perceived intensity, vividness, rehearsal, confidence and valence of their diagnosis memory. Finally, they answered a series of questions about their interactions with medical staff at the time of the diagnosis to determine how these conversations affected their recollection of the event.

The majority of respondents—nearly 80 percent—experienced a flashbulb memory after learning of their child's Down syndrome. In fact, our participants described their diagnosis memory as more vivid, intense and visceral than the ratings subjects had given to their recollection of 9/11 in another flashbulb memory study.

The flashbulb nature of these medical-diagnosis memories lingered for many years. Although we did not examine the way individual memories changed over time, as a longitudinal study would, we were able to compare recollections from decades earlier with those from a few months ago. Diagnosis memories from long ago were no less detailed than recent ones, and they were just as likely to have a flashbulb effect. Time seemed to soften the intensity of the memories, but even decades-old diagnoses were still rated as more emotional, vivid and salient than everyday recollections.

The support that the participating mothers received from medical staff also determined the emotional tenor of their memory and its persistence over time. Respondents who described positive interactions with the staff—such as a balanced delivery and additional resources and information for support—were less likely to report negative feelings when recounting the experience and saw a decrease in the memory's intensity over time.

More often, however, the mothers reported negative experiences with medical staff, including a lack of compassion, pressure to terminate their pregnancy, and pessimistic expectations about outcomes for their child and family. Many received limited or no additional resources or support systems. For those individuals, memories of the diagnosis continued to be associated with negative emotions, and the time that had elapsed had not helped lessen the impact. Mothers who had not received positive feedback could recall their diagnosis experience in specific, often haunting detail, even after 20 years.

One of the essential ethical standards of the Hippocratic oath is to do no harm. Our findings suggest that in adhering to this tenet, health professionals should focus not only on the medical procedures and treatments provided to people but also on the way patients are informed about their health and what the future might hold.

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BEHAVIOR & SOCIETY

Another Misguided "War" on Obesity

Boris Johnson's new campaign is focusing on personal responsibility rather than attacking poverty and inequality, the root causes of obesity

GETTY IMAGES

British Prime Minister Boris Johnson recently unveiled a "Better Health" campaign to combat obesity. The announcement was prompted by Johnson's bout with COVID-19, which included a stint in intensive care in April. Johnson is convinced that his reported body mass index of 36 (30 is considered obese) was responsible for the severity of his infection and is now on a mission to slim down the U.K.

Johnson's proposed interventions include banning junk food advertising before 9 P.M. to reduce the likelihood that children would be exposed to such ads, preventing stores from selling unhealthy snacks at entrances and checkouts, barring "buy one, get one free" promotions on unhealthy foods, and requiring restaurants with more than 250 employees to post calorie counts. Other measures include encouraging doctors to prescribe cycling (Johnson's favored mode of transportation) and facilitating access to weight-loss programs.

Critics of Johnson's antiobesity measures rightly charge that they are incomplete because they focus on personal responsibility rather than attacking the root causes of obesity—poverty and inequality. Others have pointed out in the past that calorie counts in restaurants have negligible effects on consumer behavior.

As a researcher and educator on the history and politics of obesity, I would also caution that Johnson and lawmakers from other countries who might follow in his footsteps should tread carefully. Weight is a delicate issue, and mishandling "wars" on fat or obesity could impair, rather than improve, the physical and mental health of people with obesity.

This is not to say we should ignore links between obesity and COVID-19. There is mounting evidence that obesity is the most significant risk factor in serious cases of COVID-19, possibly second only to age. Studies of populations in China, Italy, the U.S., France and Britain have shown that people with obesity may double their risk of being hospitalized or dying from COVID-19 and that relationships between weight and COVID-19 are particularly pronounced among younger people and men.

Forty-two percent of American adults are classified as obese.

There are a number of explanations as to why obesity can aggravate COVID-19 infections. Scientists have found that COVID-19 often enters the body through an enzyme called ACE2 and that people with fat tissue have more ACE2 receptors and are therefore more susceptible to infection and higher viral loads.

Once infected with COVID-19, some doctors have proposed that because fat tissue compresses the diaphragm and lungs, those with obesity experience greater difficulty breathing. Another popular theory is that obesity may interfere with the proper functioning of immune cells and trigger an excessive immune response called a cytokine storm, resulting in potentially life-threatening inflammation and organ failure. Some researchers have also suggested that irregular levels of hormones associated with obesity, such as glucose-regulating adiponectin and weight-regulating leptin, compromise immune responses to the virus.

Weight is a delicate issue, and mishandling "wars" on fat or obesity could impair, rather than improve, the physical and mental health of people with obesity.

As researchers continue to investigate links between obesity and COVID-19, countries and public health organizations would be well advised to devote renewed attention to obesity. In doing so, public health initiatives must learn from the mistakes of previous campaigns that stigmatized people with obesity as lazy, weak-willed and gluttons for junk food.

In 2012 both Children's Healthcare of Atlanta (Georgia's largest pediatric health care system) and Blue Cross and Blue Shield of Minnesota launched controversial ad campaigns that critics have justly characterized as fat shaming. One Georgia poster featured four overweight children, with captions such as "Big bones didn't make me this way. Big meals did." Meanwhile the Minnesota ads targeted parents. One of its commercials featured a large man at a fast-food outlet carrying a tray of burgers, hot dogs, fries, onion rings and sugary beverages. As the man blithely walked toward his booth, he overheard his overweight son in competition with another boy over whose father could eat the most. He suddenly felt ashamed.

I fear that these types of misguided ads and antiobesity campaigns might resurface in the COVID-19 era and that the pandemic will provide added ammunition to the notion that people with obesity are social and medical scourges. Overweight children may be subjected to more bullying by peers if there are Internet ads, commercials, posters and billboards stigmatizing people with obesity and their alleged diet and exercise habits.

Among adults, anonymous commentators of news stories about COVID-19 are already posting that people's fates are the result of "poor lifestyle habits," a claim reminiscent of the 1980s and early 1990s when antigay voices maintained that people died of AIDS because of the "homosexual lifestyle." Furthermore, stigmatizing people for their weight would be inimical to the current reckoning with racial injustice because African-American women and Latinx children are the most disproportionately affected by obesity in the U.S.

To those who insist that blunt messaging is necessary to underscore the gravity of obesity just as sensationalistic antitobacco ads were

needed to drive home the dangers of smoking, public health research has shown that not only is stigma ineffective, it can induce people with obesity to gain, rather than shed, pounds.

Studies have found that both children and adults subjected to weight-based bullying or discrimination are more likely to seek solace in binge eating, to develop eating disorders and to be discouraged from exercise because of anxieties about their bodies being on display. Stigmatizing people for their weight could also impair mental health and create added stress, which could result in elevated levels of the stress hormone cortisol and increased heart rate, blood pressure and weight.

To avoid these consequences, campaigns to reduce obesity should focus on the positive aspects of maintaining healthy diet and exercise habits. And because lower-income Americans and racial minorities are more likely to live in neighborhoods with comparatively fewer supermarkets and green spaces, public policy interventions should also ensure access to affordable healthy foods and spaces that facilitate exercise and recreation. Such interventions align with the consensus among obesity experts that weight is the function of the interaction between genes and the environment.

Finally, it is imperative that antiobesity initiatives also include an educational component in which the public and even health-care providers are informed about the effects of weight bias. Rebecca M. Puhl and Chelsea A. Heuer, leaders in this area of research, point to studies revealing that health professionals sometimes regard patients with obesity as "lazy, lacking in self-discipline, dishonest, unintelligent, annoying, and noncompliant with treatment" and that medical appointments with heavier patients are shorter than those with thinner patients.

Patients with obesity perceive these slights, reporting that health-care providers do not take them seriously, erroneously assume that their weight is responsible for all their ailments, and condescend to them about losing weight. Hospital gowns, examination tables and medical equipment that are not designed for larger bodies exacerbate the embarrassment and indignities they experience. As a result, patients with obesity may forgo subsequent medical care, including lifesaving cancer screenings.

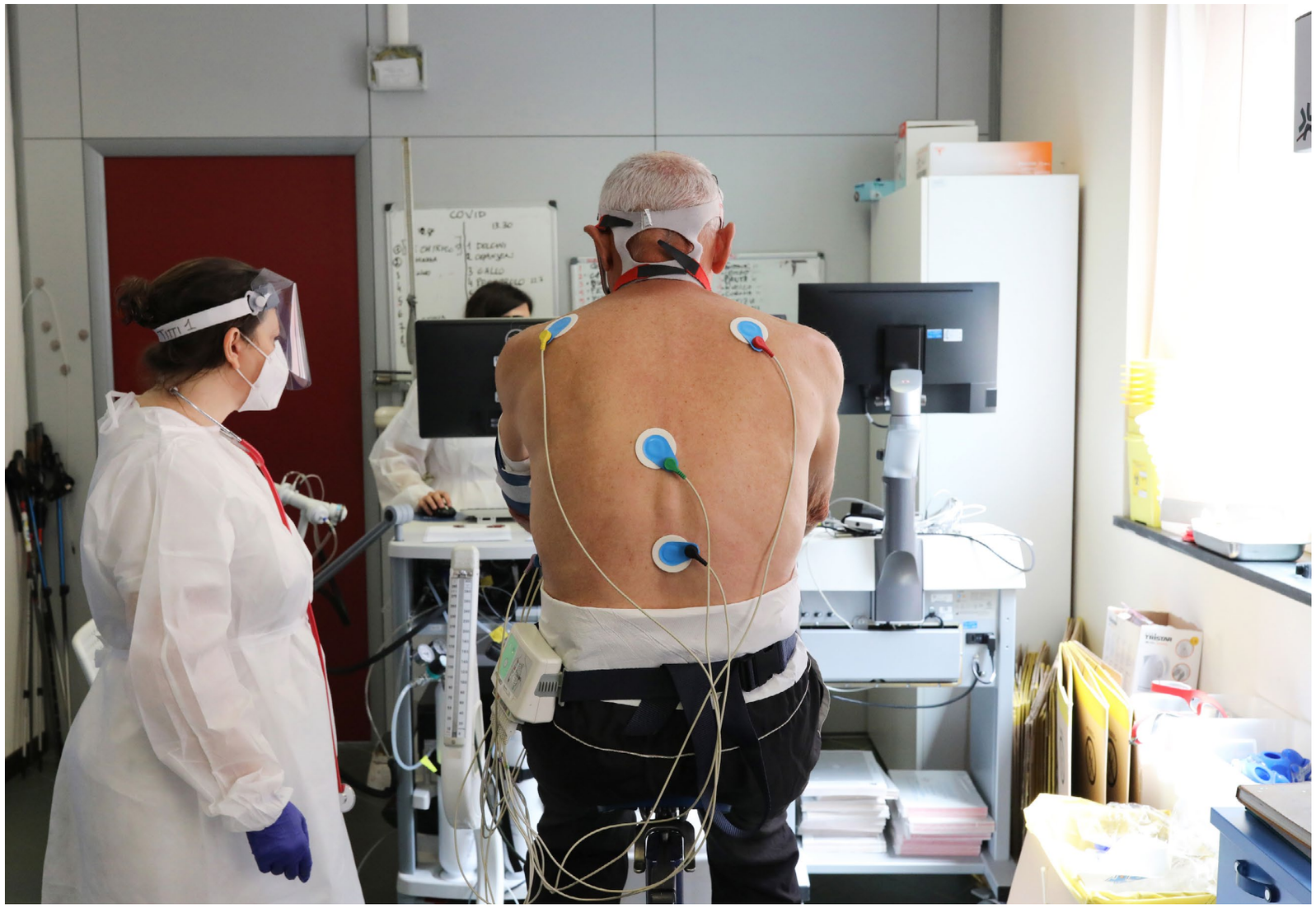
On the surface, at least, Boris Johnson seems to have come to appreciate the importance of approaching obesity with more compassion. In 2004 he wrote a newspaper column headlined "Face It: It's All Your Own Fat Fault." Now he reassures the British public that his antiobesity program is not meant to be "excessively bossy or nannying," adding: "We want this one to be really sympathetic to people, to understand the difficulties that people face with their weight, and just to be helpful."

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

THE BODY

COVID-19 Can Wreck Your Heart, Even If You Haven't Had Any Symptoms

A growing body of research is raising concerns about the cardiac consequences of the coronavirus



MARCO DI LAURO *GETTY IMAGES*

Beyond its scientific backing, the notion that a COVID-19 patient might wind up with long-term lung scarring or breathing issues has the ring of truth. After all, we hear the stories, right? The virus can leave survivors explaining how they struggled to breathe or how it can feel, in the words of actor Alyssa Milano, "like an elephant is sitting on my chest."

We've also known for a while that some COVID-19 patients' hearts are taking a beating, too—but over the past few weeks, the evidence has strengthened that cardiac damage can happen even among people who have never displayed symptoms of coronavirus infection. And these frightening findings help explain why college and professional sports leagues are proceeding with special caution as they make decisions about whether or not to play.

From an offensive lineman at Indiana University dealing with possible heart issues to a University of Houston player opting out of the season because of "complications with my heart," the news has been coming fast and furiously. More than a dozen athletes at Power Five conference schools have been identified as having myocardial injury following coronavirus infection, according to

ESPN; two of the conferences—the Big Ten and the Pac-12—already have announced they are postponing all competitive sports until 2021. And in Major League Baseball, Boston Red Sox ace pitcher Eduardo Rodriguez told reporters that he felt "100 years old" as a result of his bout with COVID and of MLB's shortened season because of myocarditis—an inflammation of the heart muscle, often triggered by a virus. Said Rodriguez: "That's [the heart is] the most important part of your body, so when you hear that … I was kind of scared a little. Now that I know what it is, it's still scary."

Why are these athletes (and their leagues and conferences) taking such extreme precautions? It's because of the stakes. Though it often resolves without incident, myocarditis can lead to severe complications such as abnormal heart rhythms, chronic heart failure and even sudden death. In August a former Florida State basketball player, Michael Ojo, died of suspected heart complications just after recovering from a bout of COVID-19 in Serbia, where he was playing pro ball.

Here's the background: Myocarditis appears to result from the direct infection of the virus attacking the heart or possibly as a consequence of the inflammation triggered by the body's overly aggressive immune response. And it is not age-specific: In the *Lancet*, doctors recently reported on an 11-year-old child with multisystem inflammatory syndrome (MIS-C)—a rare illness—who died of myocarditis and heart failure. At autopsy, pathologists were able to identify coronavirus particles present in the child's cardiac tissue, helping to explain the virus's direct involvement in her death. In fact, researchers are reporting the presence of viral protein in the actual heart muscle of six deceased patients. Of note is the fact that these patients were documented to have died of lung failure, having had neither clinical signs of heart involvement nor a prior history of cardiac disease.

"My personal take is that COVID will increase the incidence of heart failure over the next decades."
—Elike Nagel

Ossama Samuel, associate chief of cardiology at Mount Sinai Beth Israel in New York, told me about a cluster of younger adults developing myocarditis, some of them a month or so after they had recovered from COVID-19. One patient, who developed myocarditis four weeks after believing he had recovered from the virus, responded to a course of steroid treatment only to develop a recurrence in the form of pericarditis (an inflammation of the sac surrounding the heart). A second patient, in her 40s, now has reduced heart function from myocarditis, and a third—an athletic man in his 40s—is experiencing recurring and dangerous ventricular heart rhythms, necessitating that he wear a LifeVest defibrillator for protection. His MRI also demonstrates fibrosis and scarring of his heart muscle, which may be permanent, and he may ultimately require placement of a permanent defibrillator.

This is an incredibly tricky diagnosis. Patients with myocarditis often experience symptoms such as shortness of breath, chest pain, fever and fatigue—while some have no symptoms at all. J.N., a health-care provider who asked that his full name not be used, told me that COVID-19 symptoms first appeared in his case in late March. He ultimately was hospitalized at Mount Sinai Medical Center after developing unrelenting fevers spiking to 104 degrees, chest tightness, nausea, vomiting and diarrhea.

"Even the Advil and acetaminophen wouldn't help my fevers," said J.N. Just 34 years old, he was diagnosed with COVID-induced myocarditis and severe heart failure. Doctors admitted him to the intensive care unit and placed him on a lifesaving intra-aortic balloon pump because of the very poor function of his heart. He spent two weeks in the hospital, has suffered recurrences since his discharge, and now says, "I'm very careful. I'm very concerned about the length of time I've been feeling sick and if these symptoms are lifelong or will go away anytime soon." J.N. said that everyday activities, such as carrying his one-year-old daughter up a flight of stairs, leave him feeling winded and fatigued. He has been unable to work since March.

According to some reports, as many as 7 per-

cent of deaths from COVID-19 may result from myocarditis. (Others feel that estimate is too high.) The arrhythmia that sometimes accompanies it is also worrisome, and researchers have found that to be fairly common among COVID-19 patients. In J.N.'s case, he noticed his heart racing on several occasions into the 130 beats per minute range. And while the prevalence of this in virus patients is not known exactly, a study published recently in the *Journal of the American College of Cardiology* found that some type of ventricular arrhythmias occurred in 78 percent of patients without COVID. Up to 30 percent of the full study group, meanwhile, experienced serious arrhythmias 27 months later.

Experts estimate that half of myocarditis cases resolve without a chronic complication, but several studies suggest that COVID-19 patients show signs of the condition months after contracting the virus. One non-peer-reviewed study, involving 139 health-care workers who developed coronavirus infection and recovered, found that about 10 weeks after their initial symptoms, 37 percent of them were diagnosed with myocarditis or myopericarditis—and fewer than half of those had showed symptoms at the time of their scans.

Any such cardiac sequelae lingering weeks to months after the fact is clearly concerning, and we're seeing more evidence of it. A German study found that 78 percent of recovered COVID-19 patients, the majority of whom had only mild to moderate symptoms, demonstrated cardiac involvement more than two months after their initial diagnoses. Six in 10 were found to have persistent myocardial inflammation. While emphasizing that individual patients need not be nervous, lead investigator Elike Nagel added in an e-mail, "My personal take is that COVID will increase the incidence of heart failure over the next decades."

Taking on myocarditis is a chore. Thankfully, some acute cases resolve on their own, requiring only hospital monitoring and possibly some heart medications. We've learned that steroids and immunoglobulins—useful elsewhere—aren't effective in acute viral myocarditis, although Samuel said there may be a role for steroids in younger COVID-19 patients who seem to present with more of an autoimmune type of the condition. And, of course, an effective vaccine could help prevent cases in the first place.

Samuel called it "extremely dangerous" for athletes diagnosed with myocarditis to play competitive sports for at least three to six months because of the risk of serious arrhythmia or sudden death, and several athletes already have made the decision to heed those dire warnings. We'll likely see more such decisions in the very near future, as each sport enters its peak season.

And for the rest of us? Wear a mask, social distance, avoid large gatherings and spend more time in the great outdoors. I would echo the advice of J.N.: "Be careful. Just don't get the virus in the beginning." As of today, it's still the best defense we've got.

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