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all the stops to battle the
coronavirus: novel treatments,
repurposed drugs, vaccines**



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SCIENCE OF
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**HARNESSING
HUMAN IMMUNE
CELLS TO FIGHT
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WITH COVERAGE FROM
nature

LIZ TORMES



Science without the Luxury of Time

It's long been a sticking point between the public and science: a disaster befalls us unexpectedly, and we, of course, want answers immediately. But in the cruelest kind of irony, most science cannot be done in a rush. The beauty of the scientific method is its careful use of observation over time—tracking the migration patterns of birds for decades, for example. Or, when it comes to drug development, the gold-standard randomized controlled clinical trial, where an equal proportion of patients are given no treatment at all to serve as a baseline against which researchers can compare any effects of the drug being given to the other participants. These careful procedures give us the best science. They take time and a kind of cool detachment, allowing data to roll in before conclusions are drawn.

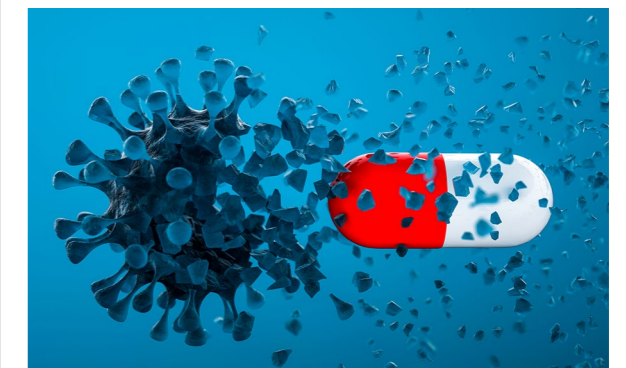
But tell that to the family of a woman in severe respiratory distress from COVID-19. Waiting to know which of the handful of potential treatments for the novel coronavirus might be effective is a privilege of time that many patients don't have. In this issue, health and medicine editor Tanya Lewis gives a detailed survey of the batch of drugs researchers are rushing to test scientifically, even as they are being put to the test on a case-by-case basis (see "[Here's What We Know about the Most Touted Drugs Tested for COVID-19](#)"). Elsewhere, journalist Stacey McKenna takes a sobering look at what researchers actually know about immunity to the virus (see "[What Immunity to COVID-19 Really Means](#)"), and biologist William A. Haseltine evaluates the limitations of a vaccine solution (see "[Can We Really Develop a Safe, Effective Coronavirus Vaccine?](#)").

The common theme to all these riveting stories? Making safe and effective medicine needs time—the one luxury we now cannot afford.

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New Coronavirus Drug Shows Promise in Animal Tests

Slated for human trials, EIDD-2801 could become the first pill for COVID-19

An oral medicine was able to hinder the coronavirus behind COVID-19 as it attempted to replicate itself in human lung cells in test tubes, scientists reported in April. It also hampered the reproduction of closely related coronaviruses in mice for several days and improved the animals' lung function.

The drug, called EIDD-2801, interferes with a key mechanism that allows the SARS-CoV-2 virus to reproduce in high numbers and cause infections, the researchers explained in the journal *Science Translational Medicine*. Human trials

have not yet been done, but if the effect is similar in people, the drug could be the first pill available to help with the COVID-19 pandemic, which had resulted in more than three mil-

lion cases and at least 225,000 deaths worldwide as of press time. An oral medication would be a boon because it would be easier to give to people than an intravenous injection.

The study was done by a team at Emory University, the University of North Carolina at Chapel Hill and Vanderbilt University Medical Center. A company that has licensed the drug,



Workers at a private manufacturing unit on the outskirts of Srinagar, India, make face masks to meet demand in view of the spread of the novel coronavirus pandemic in April 2020.

Miami-based Ridgeback Biotherapeutics, has just been granted permission from the U.S. Food and Drug Administration to begin 10 patient trials of the antiviral pill in the next few months.

The same university collaboration had already found that Gilead Sciences' experimental medicine remdesivir was effective in shutting down replication of the coronaviruses that caused the original SARS and MERS epidemics. Remdesivir has received attention because it entered clinical trials against SARS-CoV-2 in March, and the first results appeared in late April. The findings announced so far indicate that EIDD-2801 is possibly even more successful in disrupting coronavirus replication than the Gilead drug. On March 20 the researchers investigating EIDD-2801, co-led by Tim Sheahan of U.N.C. Chapel Hill, posted the results of their animal studies on the preprint server bioRxiv while submitting them for peer review. Given the current COVID-19 crisis, "it was important to share," says George Painter, a professor of pharmacology and president of the Emory Institute for Drug Development, which first produced the drug.

Back in 2018 Painter and the labs

he leads identified EIDD-2801's activity during a search for a universal influenza medicine. Last October, before the pandemic hit, the Emory program got \$15.9 million from the National Institute of Allergy and Infectious Diseases to perform human tests of the drug against the flu virus that was likely to be circulating later in the year. When SARS-CoV-2 emerged, Painter's group immediately shifted focus.

EIDD-2801 inhibits the coronavirus's self-copying operations in a manner that is different from remdesivir's. Whereas remdesivir brings that replication process to a full stop, EIDD-2801 introduces mutations—mistakes—into the virus's RNA as it makes copies, leaving the viral RNA so damaged that it cannot infect cells. Another feature of the drug is that it is able to work against a host of other RNA viruses. Thus, it could serve as a multipurpose antiviral, much in the way that some antibiotics can work against a wide variety of bacteria.

In several preclinical studies, researchers from multiple labs have shown that EIDD-2801 was effective against several strains of influenza, as well as respiratory syncytial

virus and the viruses that cause chikungunya, Venezuelan equine encephalitis and Eastern equine encephalitis—all microbes that intermittently pop up in different parts of the world and produce widespread sickness.

The compound may be initially beneficial as a "prophylaxis [that] health care workers can take to prevent an infection," says Wayne Holman, co-founder of Ridgeback, which has licensed the drug from Emory's non-profit biotech company Drug Innovation Ventures at Emory (DRIVE). Another potential use of EIDD-2801 might be to protect uninfected nursing home residents and workers if an outbreak occurs inside a facility. Holman says the wider goal is to have an oral pill that can be taken twice a day by patients at home early in the course of the disease to prevent it from progressing to hospitalization, mechanical ventilation or death.

In addition to planning clinical trials in the U.S., Ridgeback has also asked U.K. authorities to start tests there. "We've done three to four years of development work in just the past three to four weeks in response to the new pandemic," Holman says. —Michael Waldholz

The Loneliness of the "Social Distancer" Triggers Brain Cravings Akin to Hunger

A study on isolation's neural underpinnings implies many may feel literally "starved" for contact amid the COVID-19 pandemic

Loneliness hurts. It is psychologically distressing and so physically unhealthy that being lonely increases the likelihood of an earlier death by 26 percent. But the feeling may serve a purpose. Psychologists theorize that it hurts so much because, like hunger and thirst, loneliness acts as a biological alarm bell. The ache of it drives us to seek out social connection just as hunger pangs urge us to eat. The idea is intuitively satisfying, yet it has long proved difficult to test in humans.

On March 26, however, just as the COVID-19 pandemic gripped the world, researchers at the Massachusetts Institute of Technology posted a preliminary report on bioRxiv. It was the first study in humans to show

that both loneliness and hunger share signals deep in a part of the brain that governs very basic impulses for reward and motivation. The findings point to one telling conclusion: our need to connect is apparently as fundamental as our need to eat.

The extraordinary scientific timing of the paper's release—just as tens of millions of people were suddenly starved for contact—was far from intentional. When they began the work three years ago, neuroscientists Livia Tomova and Rebecca Saxe and their colleagues wanted to demonstrate how loneliness operates in the brain. They were inspired by similar research in animals and by the pioneering loneliness studies of the late University of Chicago psychologist John Cacioppo.

But enforced social isolation is so rare in healthy, nonincarcerated humans that it gave the team pause. "I sometimes struggled to articulate what that would be like in the real world," Saxe admits. "Why would that ever happen?" By the time the researchers came to write their study this year, the unimaginable had become real. Now, Saxe says, "what feels most significant about this paper is that it's a way to step out-



side the experience we're having and look on it through a different lens."

This is "a tour de force paper," says psychologist Jamil Zaki of Stanford University, who was not involved in the research. He studies empathy and social interaction and is the author of *The War for Kindness: Building Empathy in a Fractured World*. "Speculatively, it suggests that chronic social isolation might be something like long-term undernourishment, producing steady, aversive need that wears away at our well-being," Zaki says. "These findings

give a name to what countless people are experiencing right now: social craving while staying at home to protect the public health."

The paper, which has not yet been peer-reviewed, describes a carefully designed experiment using functional magnetic resonance imaging (fMRI) to compare brain responses to loneliness and hunger. After a baseline brain scan, 40 adult participants underwent two 10-hour sessions: one in which they were deprived of food and another where they were denied social contact. The

sessions served as control conditions for each other.

The social-isolation condition was challenging to arrange. Some people are lonely in a crowd, whereas others enjoy solitude. To induce not just objective isolation but subjective feelings of loneliness, the researchers had the participants spend their time from 9 A.M. to 7 P.M. in a sparsely furnished room at the laboratory without phones, laptops or even novels, in case fictional characters provided some social sustenance. Puzzles were allowed, as was

preapproved nonfiction reading or writing. During the food-deprivation day, the subjects could not eat or drink anything but water over the same time frame.

Brain scanning immediately followed each deprivation session, yet measuring the relevant brain signals was also challenging. Tomova and Saxe focused on a midbrain region called the substantia nigra, a center of dopamine release involved with motivation and craving. Because an fMRI signal from the substantia nigra is indirect, the researchers designed a cue-induced craving task similar to what is used in addiction research. When drug addicts are shown cues associated with their substance of choice, “they show a really strong wanting response,” Tomova says. “It’s quite established that this triggers this dopaminergic response.”

In the scanner, the participants saw images of their preferred forms of social interaction and of their favorite foods, as well as a control image of flowers. “We found that this brain area specifically responded to the cues after deprivation but only to cues of what they had been deprived of,” Tomova says. The magnitude of the response correlated with the sub-

jects’ self-reports of how hungry or lonely they were, although feelings of hunger were consistently stronger.

Finally, the researchers used machine learning to confirm their findings. A software classifier trained to recognize neural patterns during fasting proved able to recognize similar neural patterns from the social-isolation condition even though it had never “seen” them. “This tells us that there seems to be an underlying shared neural signature between the two states,” Tomova says. “Social contact is a very basic need.”

Even before the COVID-19 pandemic, an obvious next question for the work was whether different forms of social media could satisfy the need for social connection. Saxe and Tomova were never able to get funding for such a study. It seems likely they will now. Tomova is already working with researchers at the University of Cambridge, where she will move in the fall, to see if social media use during the pandemic might be remediating feelings of loneliness. “Twenty years from now,” Saxe says, “we will know what all the effects were of this experience we are having.” —Lydia Denworth

Could Newly Found “Peacekeeping” Cells Be a Weapon against COVID-19?

In mice, these white blood cells tamp down inflammation in the lungs

To fight a respiratory infection, the body needs a two-pronged attack. First it sends immune cells to the scene to destroy the pathogen. Then the defense system must keep those first responders from spiraling out of control. If this attempt at “peacekeeping” fails, a run-of-the-mill fever and cough can escalate to a life-threatening illness—which happened to the hundreds of thousands of COVID-19 patients who have succumbed to the global pandemic caused by the SARS-CoV-2 virus.

For the most part, macrophages—large immune cells that consume pathogens—are the first responders. In the lungs of mice infected with viral influenza, however, a small subset of these white blood cells do just the opposite: they suppress excess inflammation, researchers reported

in March in the journal *Science Immunology*. These peacekeeping macrophages also reside in human lungs, suggesting they “might be very important to help COVID-19 patients resist inflammation and maybe survive,” says immunologist Yufang Shi of the First Affiliated Hospital of Soochow University in China. The hospital sent staff and supplies to the nation’s city of Wuhan, but Shi was not involved in the new study.

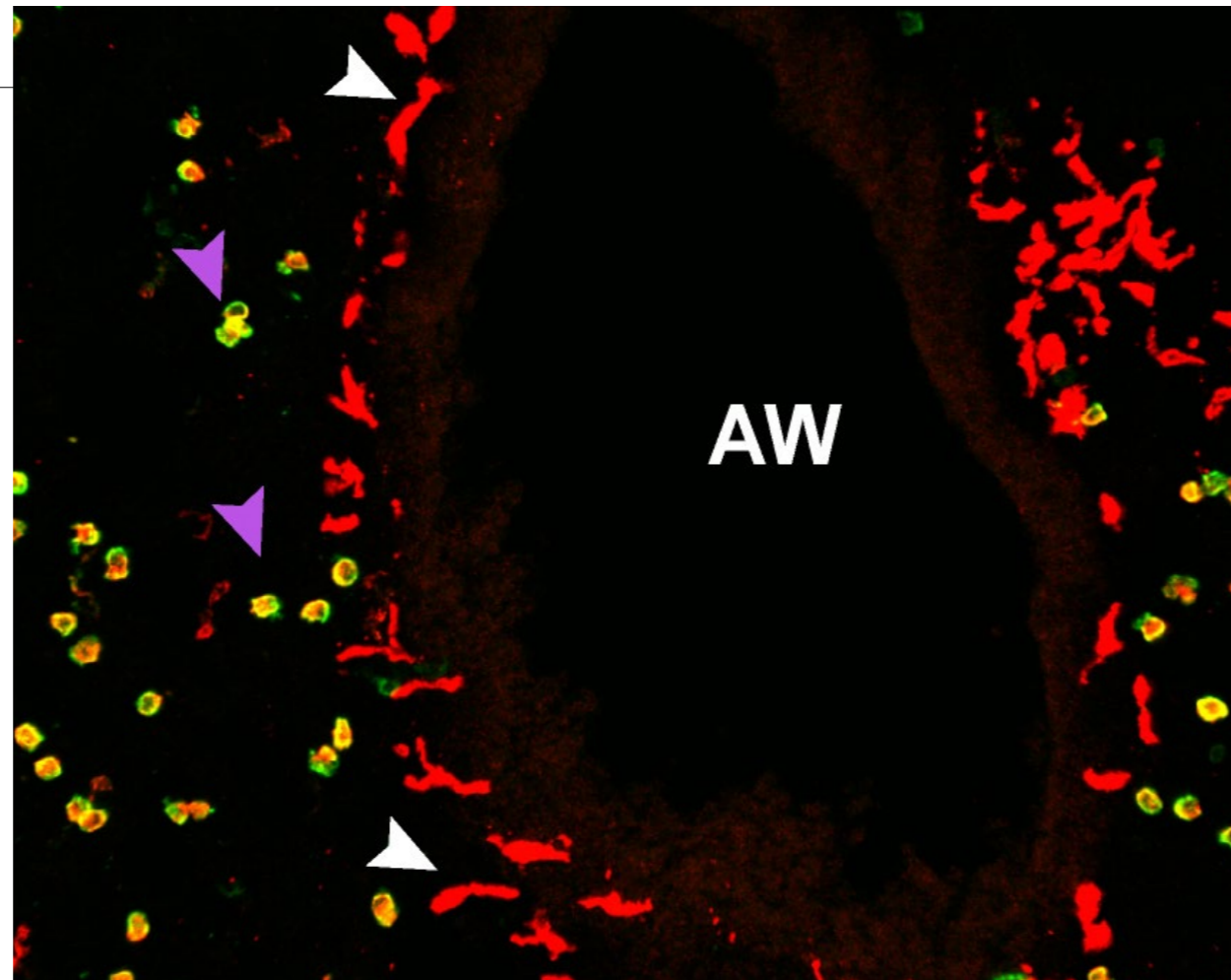
The research began seven years ago, when Kamal Khanna, an immunologist now at N.Y.U. Langone Health, noticed something he found to be stunning. At the time, his lab was studying a similar group of macrophages—not in the lungs but in the spleen, a blood-filtering organ in the lymphatic system. On stained mouse tissue viewed under a microscope, the macrophages formed blue rings around immune cell-rich areas of the spleen. “They looked like nebulas,” Khanna says.

And these cells were not just visually impressive. When the researchers depleted the macrophages using a clever genetic strategy, the mice died just two days after being infected with small amounts of *Listeria*

bacteria they would normally clear. Another observation was also striking: whereas other immune cells packed infection-fighting zones in the spleen, this group of macrophages stayed put. “And we thought that this compartmentalization has to be present in [nonimmune] organs as well,” Khanna says. The spleen findings, [published in 2017](#), laid the groundwork for the new analysis in lungs.

In this complex organ, the vast majority of macrophages live in tiny air sacs called alveoli. But when the researchers examined the lung tissue under a microscope, they saw a much smaller population that was starkly different. Unlike alveolar macrophages (AMs), which are large and round, the rarer macrophages are elongated with sprawling arms—and they are not found in alveoli. Called nerve- and airway-associated macrophages, or NAMs, these newly identified cells congregate at airways and interact with surrounding nerves. “The whole airway branch gets lit up with these macrophages,” Khanna says.

In another set of studies, his team depleted mice of AMs or NAMs. They then infected those animals and nor-



Section of mouse lungs with white arrows pointing to nerve- and airway-associated macrophages (NAMs) and purple arrows indicating alveolar macrophages (AMs). (AW denotes airway.)

mal mice with an influenza virus and compared the virus levels in the two groups. The experiments revealed a division of labor: AMs help to fight the virus; NAMs keep the peace and prevent tissue damage.

This kind of differentiation could prove important for designing therapies targeted at inflammation, which is a big problem in COVID-19, says Mallar Bhattacharya, a macrophage biologist at the University of California, San Francisco, who was

not involved with the research but calls it a “clever application of novel tools for deletion of specific macrophage subsets.”

NAM-depleted mice produced higher levels of several inflammatory molecules, including one called IL-6 that is involved in the so-called [cytokine storms](#) seen in some patients with severe COVID-19. In a recent [study](#) of 191 people treated for it in Wuhan, blood IL-6 levels were elevated in patients who died of the

disease compared with those of survivors. [Clinical trials](#) are now evaluating IL-6-blocking antibodies—drugs used to treat rheumatoid arthritis—in COVID-19 patients.

The new study did not address how the intertwining of NAMs with nerves relates to the function of these immune cells. Khanna hopes to gain insight in future mouse studies by depleting NAMs and assessing the health of surrounding nerves or by examining how the airway nerves are affected during different types of infections. The nervous-immune connection is intriguing in light of recent research suggesting that chemical cross talk between gut macrophages and nerve fibers can [control peristalsis](#), the process that moves food through the digestive tract.

A more pressing question is whether NAMs are involved in COVID-19. To answer it, Khanna is working with N.Y.U. Langone Health to obtain fresh lung tissue from people who died of the disease—but doing so is logistically hard and possibly risky. An even bigger challenge for now, in light of New York City’s rising number of cases, is that “basically, our lab is shut down,” Khanna says.

—Esther Landhuis

Decoding the Vaginal Microbiome

The most detailed map of its kind catalogues the sequences of about a million bacterial, viral and fungal genes

Mention the term “microbiome,” and most people will quickly think of the gut, probiotics and maybe even fecal microbial transplantation. But it actually refers to all the genetic material found in the microbes that live on and in the human body, including yeasts, bacteria and viruses. The vagina has a microbiome, too—even if research on it is lagging behind that done on the microbiomes of other parts of the body.

Progress in this area may soon speed up, however, because in February researchers at the University of Maryland School of Medicine announced a new tool that maps the vaginal microbiome with unprecedented resolution. Named VIRGO (which stands for “human vaginal non-redundant gene catalog”), it is the culmination of data collected from many different studies conducted over the past decade. The tool in-



Lactobacillus crispatus bacteria illustration

cludes the sequences of roughly one million genes in bacteria, viruses and fungi that are active in the vagina.

“The effort will be important for accelerating discoveries into new diagnostic tests and treatments [for vaginal health conditions],” says Jennifer Fettweis, a microbiologist and director of the Vaginal Human Microbiome Project at Virginia Commonwealth University. Fettweis, who

was not involved with the new study, explains that the publicly available VIRGO database will help accelerate progress in the field. “I think what [the paper’s authors have] done here is really important on that front,” she says.

Research efforts over the past decade, including the Human Microbiome Project, have illuminated the extent to which microbes inhabit our

bodies. Current estimates show that there are roughly the same number of bacterial cells in the body as human cells.

And these bacterial cells are not just passively sitting around. In the gut, microbes are involved in a variety of essential operations, such as digestion, immune system function and even the production of vitamins. Scientists believe microbes play

equally important roles in the vagina but have not yet been able to elucidate their functions. Many hope VIRGO will change that situation.

The researchers assembled the tool by combining metagenomic data from 264 vaginal swab samples obtained by the University of Maryland team with the full genome sequences of 308 vaginal bacterial strains. They sequenced the samples using metagenomic techniques, which allowed the scientists to identify the microbial composition, and metatranscriptomic ones, which provided information on what genes were active. The result is a database with more than a million bacterial genes that represent 300 different species present in the vagina.

In one of the earliest examples of its applications, scientists showed how VIRGO can be used to understand the mechanism of an intractable vaginal disorder. During the study, one woman developed a case of bacterial vaginosis—a disorder caused by the overgrowth of harmful bacteria that produces uncomfortable symptoms and, sometimes, serious complications, including preterm birth and infertility.

Using data collected from the

woman's vaginal samples at different points throughout the infection, the researchers were able to map out exactly how bacterial gene activity fluctuated during its course. Just before symptoms started there was an increase in the activity of a bacterial species called *Lactobacillus iners*. This species made up only 1 percent of the microbial community, but it was extremely active, producing 20 percent of the gene products present in the sample. Even though this observation was based on just a single patient, *L. iners* has previously been associated with bacterial vaginosis in larger studies. It was the first time the microbe's activity was shown to increase prior to the development of symptoms, however.

"This was a major finding," says Jacques Ravel, a microbial genomicist at the University of Maryland School of Medicine and senior author of the study. He explains that VIRGO's ability to see the functional contributions of microbes even when they are relatively scarce is a strength of the tool. Ravel, who is also co-founder of and chief scientist at LUCA Biologics—a biotechnology company that works to develop live therapeutics for wom-

en's health—sees potential in using VIRGO to develop diagnostic tests as well.

According to Molly Stout, an obstetrics researcher at Washington University School of Medicine in St. Louis, who was not involved in the study, "[the tool] not only addresses who is there in the [bacterial] community but also what are they doing." Fettweis agrees. She and her team have been working hard "to fill in the dark matter" on the vaginal microbiome, she says. In 2012 she and her colleagues published a database that catalogued all the bacteria species present in the vagina. She says VIRGO adds a deeper level of resolution that can distinguish strains within a species.

To understand why it is important to identify bacterial strains, consider the common species *Escherichia coli*. It has hundreds of strains. Many of them live in the intestines of humans and animals and are considered healthy, with some aiding in food digestion. But many others—at least 200—are pathogenic, causing foodborne illnesses, diarrhea, urinary tract infections and even some forms of meningitis.

Individual strains could mean the

difference between health and disease in the vagina as well. *Lactobacillus crispatus* has long been considered the hallmark of a healthy vagina because of its role in producing lactic acid, which maintains a protective acidic environment. But with the help of VIRGO, scientists saw, for the first time, that not all *L. crispatus* strains are the same—there was enormous diversity in gene expression among them.

"What this implies is that *L. crispatus* in one woman is very different from *L. crispatus* in another," Ravel says. This finding could shake up current efforts that involve designing probiotics based on bacterial sequences. Ravel explains that every strain could have a different function and that this idea is a "completely new way of viewing the vaginal microbiome."

Fettweis hopes databases such as VIRGO will help pave the future path for women's health. She thinks that as more and more groups build catalogues and make their data publicly available, the progress on the vaginal microbiome will accelerate. "The ultimate goal would be to pool all of [the information] together," she says. —Monique Brouillette

Here's What We Know about the Most Touted Drugs Tested for COVID-19

Numerous contenders—from a controversial malaria medication to treatments that regulate the immune system—are now in clinical trials

By Tanya Lewis



Tanya Lewis is an associate editor at *Scientific American* who covers health and medicine.

AS THE COVID-19 PANDEMIC CONTINUES TO CLAIM LIVES AROUND THE WORLD, there are no specific treatments for the disease beyond supportive care. Several drugs already prescribed for other illnesses have shown promise against the novel coronavirus in preclinical studies, and they are now being tested in clinical trials or given to patients on a compassionate-use basis. But experts warn that these medications have yet to prove effective in treating COVID-19 patients.

As of press time, the virus has infected more than three million people worldwide and caused more than 225,000 deaths. A vaccine and new treatments could take years to fully develop, but the World Health Organization recently launched a large international trial called Solidarity to test four existing therapies. They are the closely related malaria drugs chloroquine and hydroxychloroquine; the antiviral medication remdesivir (originally developed to treat Ebola); the antiviral combination of lopinavir and ritonavir (used for HIV); and those two HIV drugs plus the anti-inflammatory small protein interferon beta. A number of separate clinical trials of these medications and others are underway in several countries, including the U.S.

The U.S. Food and Drug Administration has approved remdesivir for treating COVID-19 patients under the compassionate-use protocol (a designation that gives patients who have life-threatening illnesses access to an experimental drug). In addition, the agency has granted an emergency-use authorization—which allows for otherwise unapproved drugs or uses during an

emergency—for chloroquine and hydroxychloroquine.

“None of these therapies are proven,” says Stanley Perlman, a professor of microbiology and immunology at the University of Iowa. Only the results of randomized clinical trials can show whether they work, he adds.

Here is what scientists know so far about some of the most prominent drugs currently being tested as treatments for the potentially deadly infection.

CHLOROQUINE AND HYDROXYCHLOROQUINE

President Donald Trump has repeatedly touted the malaria drugs chloroquine and hydroxychloroquine as a treatment for COVID-19—despite a lack of clinical evidence that they work for the disease. The president’s comments set off a scramble among doctors and patients to obtain the drugs—which are frequently used to treat autoimmune diseases such as rheumatoid arthritis and lupus—and there is now a shortage of them in the U.S. These substances can be dangerous in healthy people: a man in Arizona died after ingesting a fish-tank cleaner

containing a type of chloroquine that is not approved for human use. On March 28 the FDA issued an emergency authorization for administering chloroquine or hydroxychloroquine to COVID-19 patients—but many experts say the widespread use of these drugs is premature.

“The clinical support is very, very minimal,” says Maryam Keshtkar-Jahromi, an assistant professor of medicine at the Johns Hopkins University School of Medicine, who co-authored an article in the *American Journal of Tropical Medicine and Hygiene* calling for more randomized controlled trials of chloroquine and hydroxychloroquine. The drugs do “not show strong evidence at this point,” she adds.

A few preclinical studies have suggested that these compounds could be effective at blocking infection by the novel coronavirus (officially called SARS-CoV-2), but there has been very little good evidence from clinical trials in patients with the illness it causes, COVID-19. A controversial small, nonrandomized trial of hydroxychloroquine combined with the antibiotic azithromycin in France suggested that COVID-19 patients given the treatment had lower viral loads compared with those who refused the drugs or those at another hospital who did not receive them. But experts have questioned the study’s validity, and the society that publishes the journal in which it appeared has issued a statement of concern about the results, according to Retraction Watch. (SCIENTIFIC AMERICAN reached out to the paper’s authors for comment but did not hear back from them.) A preprint study in China also claimed to show that hydroxychloroquine benefited COVID-19 patients, but it had sig-

nificant methodology problems, Keshtkar-Jahromi says. The issues included confounding variables, such as the fact that all the subjects received other antiviral and antibacterial treatments.

Some scientists say the preclinical evidence is strong enough to support chloroquine's use, however. "We know how it acts at the cellular level against the virus. We have preclinical proof," says Andrea Cortegiani, an intensivist and researcher in the departments of anesthesia and intensive care and of surgical, oncological and oral sciences at the University of Palermo in Italy. "Second, it's a cheap drug available all over [the] world," adds Cortegiani, who is also a clinician at University Hospital "Paolo Giaccone" in Italy.

Chloroquine and hydroxychloroquine have been hypothesized to work against COVID-19 by changing the pH required for SARS-CoV-2 to replicate. Given their use in autoimmune disorders, these medications could also play a role in dampening the immune response to the virus—which can be deadly in some patients.

But these drugs' cardiac toxicity is a concern, Keshtkar-Jahromi says. There have been some reports of myocarditis, or inflamed heart tissue, in people with COVID-19 who have not taken chloroquine or hydroxychloroquine. If patients receiving one of these medications die of heart complications—and are not in a clinical trial—doctors cannot know if the drug contributed to a higher chance of death.

A drug that modulates the immune response could also make someone more vulnerable to other viral or bacterial infections. "It's a double-edged sword," says Sina Bavari, chief science officer and founder of Edge BioInnovation Consulting in Frederick, Md., who, with Keshtkar-Jahromi, co-authored the article in the *American Journal of Tropical Medicine*. Administering a drug to suppress the immune system has to be done with extreme care.



Medical worker wearing a protective face mask and scrubs tends to a patient diagnosed with COVID-19 in the intensive therapy unit at Sant Pau Hospital in Barcelona on April 2, 2020.

"We are not saying, 'Don't [prescribe chloroquine],'" Bavari says. "We are saying, 'More data are needed to better understand how the drug works—if it works.'"

REMDESIVIR

This experimental antiviral drug was developed to treat Ebola, and it has been shown to be safe for use in humans. It is a broad-spectrum antiviral that blocks the replication of several other coronaviruses, according to studies in mice and in cells grown in a lab. In addition to the WHO investigation, at least two trials in China and one in the U.S. are currently evaluating remdesivir in COVID-19 patients. Results for the Chinese trials are expected later this month.

"As of this moment, we don't have data for remdesivir in human COVID-19 disease," says Barry Zingman, a professor of medicine at Albert Einstein College of Medicine and clinical director of infectious diseases at Montefio-

re Health System's Moses Campus. The two related institutions, both located in New York City, recently joined a nationwide clinical trial of the drug. "Our patients are randomized, so we don't know who's getting the drug or a placebo. [But] we have seen some patients do remarkably well," Zingman says. Trial results are on track for publication sometime in the next six to eight weeks, he adds. Later, on April 29, Gilead Sciences, the company that manufactures remdesivir, announced that data from the phase III clinical trial of the drug were "positive" and that the study had "met its primary end point." The data have not yet been released, but Gilead says it plans to submit them to a peer-reviewed journal in the coming weeks.

AS SCIENTIFIC AMERICAN reported previously, remdesivir works by inhibiting an enzyme called an RNA-dependent RNA polymerase, which many RNA viruses—including SARS-CoV-2—use to replicate their genetic

material. Timothy Sheahan of the University of North Carolina at Chapel Hill and his colleagues have shown that the drug is effective against the coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively, as well as some of the viruses behind the common cold. The team is currently in the process of testing the drug's efficacy against SARS-CoV-2. A recent study of compassionate use of remdesivir in 53 patients with severe COVID-19 found that 63 percent of those taking the drug improved, but it was not a randomized controlled trial.

"Remdesivir has some chance," Perlman says. "If we can give [the drug] early in the disease course, it could work." To know for sure, scientists must await the results of the ongoing clinical trials.

One limitation with remdesivir is that it must be given intravenously, so patients can get it only in hospitals. Sheahan and his colleagues at Emory University have recently developed a related drug called EIDD-2801, which can be taken in pill form. Like remdesivir, the medication works as a nucleoside analogue, interfering with viral replication. It was effective at preventing SARS-CoV-2-infected lung cells from replicating in a lab dish and related viruses from doing so in mice.

RITONAVIR AND LOPINAVIR

The HIV drugs ritonavir and lopinavir (sold as a combination therapy by AbbVie under the brand name Kaletra) have been tested against COVID-19 in a few clinical trials. The initial data have not shown them to be effective, however. A study in the *New England Journal of Medicine* found they conferred no benefit beyond standard care.

The drug combination is what is known as a protease inhibitor, and it works by blocking an enzyme involved in viral replication. But its action is specific to HIV and so is unlikely to work for SARS-CoV-2, Perlman says. "If you have the key to a car and you try to put it in your

“There is a long-lasting rationale for the use of convalescent plasma against any infectious disease.”

—*Andrea Cortegiani*

car, the odds of it working are one in a million," he says. "Kaletra [targets] a completely different lock" than the one for COVID-19.

Nevertheless, the WHO trial includes a group of COVID-19 patients who will receive these drugs on their own, as well as a group that will receive them in combination with interferon beta, a small cell-signaling molecule used to treat multiple sclerosis. The molecule is a "massive orchestrator of immune response," Perlman notes, so it must be used carefully. In mouse studies of the SARS and MERS coronaviruses, it halted the infections when administered early. When it was given later, he says, the mice died. Using a drug that activates the immune system could be helpful in the beginning of an infection, but giving it too late could be deadly.

IMMUNE SYSTEM INHIBITORS

Researchers are also considering a number of other therapies that tamp down the rampant immune response seen in severe COVID-19 cases. Such a flood of immune cells in the lungs—known as a cytokine storm—can lead to death. Many of the sickest patients have elevated levels of an inflammatory protein called interleukin-6 (IL-6). Research in China has suggested that Actemra (tocilizumab), an IL-6-blocking antibody drug made by Roche, shows promise against COVID-19. And Chinese authorities have recommended the drug in their treatment guidelines. Roche

has since initiated a phase III randomized controlled clinical trial for the medication. In the U.S., Michelle Gong—chief of the division of critical care at Montefiore and Albert Einstein and director of critical care research at Montefiore—and her colleagues are among dozens of groups conducting a double-blind, placebo-controlled clinical trial of a related drug called sarilumab, which is already approved for treating rheumatoid arthritis. Sarilumab will only be given to the sickest individuals: to be part of the trial, patients must be hospitalized with COVID-19 and in severe or critical condition.

CONVALESCENT PLASMA

Another treatment approach involves injecting COVID-19 patients with blood plasma from people who have recovered from the illness. The FDA recently issued guidance on the investigational use of such "convalescent plasma," which contains antibodies to the coronavirus, and clinical trials are underway.

Blood from disease survivors has been used as a treatment throughout history—from polio-infected horses in the 1930s to former Ebola patients in 2014. "There is a long-lasting rationale for the use of convalescent plasma against any infectious disease," Cortegiani says. One problem, however, is that scientists do not know whether people develop strong immunity against SARS-CoV-2. And it is not easy to collect plasma containing enough antibodies, he adds. Another issue is the shortage of eligible donors. Some companies are looking into ways to produce these antibodies artificially. In the meantime, a number of hospitals are searching for volunteers to donate plasma.

None of the therapies described above has yet been proved to treat COVID-19. But some answers can be expected in the next few weeks and months as the results of clinical trials emerge. Until then, Cortegiani says, "we cannot say, 'This drug is more promising than the other one.' We can only say, 'There is a rationale for it.'"

Researcher in Shanghai, China, employs a test for antibodies. Such tests could help determine who is immune to the coronavirus.

What Immunity to COVID-19 Really Means

The presence of antibodies to the SARS-CoV-2 virus could provide some protection, but scientists need more data

By Stacey McKenna

THE U.S. FOOD AND DRUG ADMINISTRATION RECENTLY GRANTED AN “EMERGENCY-use authorization” of a blood test for antibodies against SARS-CoV-2, the novel coronavirus that causes COVID-19. It is the first such test to receive approval for the U.S. market. And it comes at a time when health experts and leaders are embracing immunity as a potential end point to the pandemic. In Colorado a company that makes a coronavirus antibody test has donated kits to the state’s San Miguel County so that everyone there can be tested if they want to. And in Italy politicians want to use antibody status to determine which people will get “back to work” passes.

Several ambitious surveys to test for these antibodies have now been launched around the globe. The World Health Organization’s Solidarity II study will pool antibody data from more than half a dozen countries. In the U.S. a collaborative multiyear project aims to provide a picture of nationwide antibody prevalence. Its first phase is already underway, with samples being collected from blood donors in six major urban areas, including New York City, Seattle and Minneapolis. The effort will evolve into three national surveys of donors supported by the Centers for Disease Control and Prevention and conducted this fall and in the fall of 2021.

Unlike diagnostic tests, which are used to confirm the presence and sometimes the load, or amount, of the virus, antibody tests help to determine whether someone was previously infected—even if that person never showed

symptoms. Widespread use of such assays could give scientists greater insight into how deadly the virus is and how widely it has spread throughout the population.

It is less clear what those antibody tests mean for real life, however, because immunity functions on a continuum. With some pathogens, such as the varicella zoster virus (which causes chicken pox), infection confers near-universal, long-lasting resistance. Natural infection with *Clostridium tetani*, the bacterium that causes tetanus, on the other hand, offers no protection—and even people who get vaccinated for it require regular booster shots. On the extreme end of this spectrum, individuals infected with HIV often have large amounts of antibodies that do nothing to prevent or clear the disease.

At this early stage of understanding the new coronavirus, it is unclear where COVID-19 falls on the immuni-

Stacey McKenna is a medical anthropologist and freelance journalist who writes about science, travel, and all things equine.

ty spectrum. Although most people with SARS-CoV-2 seem to produce antibodies, “we simply don’t know yet what it takes to be effectively protected from this infection,” says Dawn Bowdish, a professor of pathology and molecular medicine and Canada Research Chair in Aging and Immunity at McMaster University in Ontario. Researchers are scrambling to answer two questions: How long do SARS-CoV-2 antibodies stick around, and do they protect against reinfection?

Early on, some people—most notably U.K. prime minister Boris Johnson (who later caught the virus and spent days in intensive care) and his government’s scientific adviser Patrick Vallance—touted hopes that herd immunity could be an eventual means to end the pandemic. And although it appears that recovered COVID-19 patients have antibodies for at least two weeks, long-term data are still lacking. So many scientists are looking to other coronaviruses for answers.

Immunity to seasonal coronaviruses (such as those that cause common colds), for example, starts declining a couple of weeks after infection, and within a year some people are vulnerable to reinfection. That observation is disconcerting when experts say it is unlikely we will have a vaccine for COVID-19 within 18 months. But studies of SARS-CoV—the virus that causes severe acute respiratory syndrome, or SARS, which shares a considerable amount of its genetic material with SARS-CoV-2—are more promising. Antibody testing shows that SARS-CoV immunity peaks at around four months and offers protection for roughly two to three years. As Preeti Malani,

chief health officer and professor of medicine at the University of Michigan, said in a [video interview](#) with *JAMA*'s editor in chief Howard Bauchner, this period presents “a pretty good time line for thinking about vaccines and therapeutics” for COVID-19.

Even if the antibodies stick around in the body, however, it is not yet certain that they will prevent future infection. What we want, Bowdish says, are [neutralizing antibodies](#). These are the proteins that reduce and prevent infection by binding to the part

of a virus that connects to and “unlocks” host cells. They are relatively easy to detect, and they are far easier for vaccine developers to generate than the alternative: the immune system’s T cells. In contrast, nonneutralizing antibodies still recognize parts of the pathogen, but they do not bind to it effectively and so do not prevent it from invading cells.

“If humans naturally make neutralizing antibodies [against SARS-CoV-2], then all we have to do is figure out what [sites they are] binding on the virus and really target that one little piece of protein, and that’s our magic bullet,” Bowdish says. For SARS-CoV-2, that target site is most likely on the so-called [receptor-binding domain](#) of its [spike glycoprotein](#)—a protein attached to a sugar that the virus uses to enter cells. But, Bowdish says, this spot may present a challenge because human immune systems are not very good at making antibodies against sugar-coated substances.

Nevertheless, a few small [studies of cells in laboratory dishes](#) suggest that SARS-CoV-2 infection triggers the production of neutralizing antibodies. And [animal](#)

“If humans naturally make neutralizing antibodies [against SARS-CoV-2], then all we have to do is figure out what [sites they are] binding on the virus and really target that one little piece of protein, and that’s our magic bullet.”

—*Dawn Bowdish*

remain. One [study](#) found no correlation between viral load and antibody presence, leading the authors to question the antibodies’ actual role in clearing the virus in humans. In addition, peer-reviewed research on [SARS-CoV](#) and preprint studies on [SARS-CoV-2](#) report that some nonneutralizing coronavirus antibodies might trigger a harmful immune response on reinfection with those pathogens or cross-infection with other coronaviruses. Thus, while much of the emerging research is promising, Bowdish cautions against using antibody testing to drive policy until researchers know the proportion of COVID-19 survivors who are producing neutralizing antibodies.

In an ideal world, SARS-CoV-2 immunity would resemble that acquired by children who get chicken pox. Early research suggests we are in for a much more complex scenario but one that time and unprecedented global cooperation might be able to untangle. Eventually antibody tests could be the key to getting our lives and economies back on track. For now, they promise to give experts, officials and citizens a clearer picture of the pandemic.

studies indicate that such antibodies do prevent reinfection, at least for a couple of weeks. Furthermore, because some antibodies seem to recognize and react to the [spike proteins on multiple coronaviruses](#), including SARS-CoV and MERS-CoV (the virus that causes Middle East respiratory syndrome, or MERS), researchers can build on knowledge learned from previous outbreaks.

Research on real-life immunity to SARS-CoV-2 is in its preliminary stages, and uncertainties

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Can We Really Develop a Safe, Effective Coronavirus Vaccine?

We don't know for sure, but if we can, it probably won't be easy, cheap or fast

By William A. Haseltine

IN THE EVENT OF ANY INFECTIOUS DISEASE OUTBREAK, OUR MINDS TURN TO VACCINES—and they do so for good reason. Vaccines are safe, are relatively inexpensive and have worked well for diseases including smallpox, polio, yellow fever and, most recently, Ebola.

Will a vaccine come as easily for the novel coronavirus? The answer is maybe yes, maybe no. The “maybe yes” comes from the observation that in animal studies, coronaviruses stimulate strong immune responses that seem capable of knocking out the virus. Recovery from COVID-19 may be in large part due to effective immune response. The “maybe no” comes from evidence just as strong, at least with earlier SARS and MERS viruses, that natural immunity to these viruses is short-lived. In fact, some animals can be reinfected with the very same strain that caused infection in the first place.

This raises more crucial questions with equally ambiguous answers. If a vaccine does prove to be effective, will it be effective for long? At this point, we cannot be sure. How long will it take to develop it in the first place? We can hope, but cannot be certain, that it will be developed rapidly.

To understand this better, it is important to understand how the body protects itself from invading organisms.

HOW YOUR BODY PROTECTS YOU FROM DISEASE

Certain physical and chemical barriers—skin, mucus,

stomach acid—protect the body from infection around the clock. The first line of defense is innate immunity, an immediate and nonspecific immune response to the multitudes of foreign viruses and bacteria, or pathogens, we encounter every hour of every day. This includes defenses, the ancient antimicrobial proteins that mobilize cellular pathways in the fight against pathogens, and macrophages, the white blood cells that scavenge and devour all things foreign. The ultimate goal of an innate immune response is to be broadly effective. In this regard it usually succeeds, but not always.

The second line of defense is adaptive immunity, whereby the body develops a long-lasting protective response specific to what it has seen before. It weaponizes two branches of the immune system: antibody-producing B cells, and T cells that attack and kill invading microorganisms or cells affected by those microorganisms. In many cases, adaptive immunity to a disease is long-lived—sometimes lasting a lifetime, often lasting 10 years or more. Other times the immune response is short-lived, as appears to be the case in early experiments with the novel coronavirus.

Not everyone can bear to ride out the two to eight

William A. Haseltine recently returned from Wuhan, where he chaired the ninth U.S.-China Health Summit. He is a former Harvard Medical School professor and a founder of the university's cancer and HIV/AIDS research departments. He also serves as chair and president of the global health think tank ACCESS Health International. Haseltine was at the heart of the U.S. responses to the HIV/AIDS and anthrax crises.

weeks it takes for adaptive immunity to phase into completion—which is where vaccination comes in. Vaccines prevent disease by simulating infection, teaching the immune system to recognize, remember and fight a given pathogen before actual infection occurs. Rather than unleashing virulent organisms into the body, a vaccine builds immunity by using antigens, the virtually harmless molecules that dwell on pathogenic surfaces. Antigens are foreign enough to trigger antibody production but not dangerous enough to cause disease. Thanks to vaccination, what the body would normally learn the hard way—unexpectedly, painfully and at great cost—it can now absorb under controlled conditions with relative ease.

TYPES OF VACCINES

There are many ways to develop a vaccine that successfully deters infectious disease. The first vaccine to be invented, for smallpox, used a live vaccinia virus—one similar enough to the original infectious agent but not quite identical. Unlike its disease-causing counterpart, which killed about 300 million people in its heyday, the vaccinia virus caused only mild symptoms in healthy people. We can replicate this method by identifying a “lookalike” virus that triggers the desired immune response without actually inflicting disease.

An attenuated strain of the virus, such as the one used to develop the yellow fever vaccine, is another option. Because the virus is still alive, albeit weakened, it gives the body a lasting education on how to neutralize it. The pro-

fective immunity that results could last decades. The main problem with this kind of vaccine is that not everyone has an immune system healthy enough to handle the live virus, no matter how feeble it has become.

In killed vaccines such as the polio vaccine, the virus has been inactivated and thus cannot replicate, meaning usually several doses must be administered over time.

Subunit vaccines, such as those available for hepatitis B and the human papillomavirus (HPV), inject particular parts of the virus into the muscles. They are usually administered with adjuvants, boosters that cause inflammation to strategically flood the injection site with immune cells. Unlike other vaccine types that can cause complications or even death in people with chronic immunodeficiencies or other comorbidities, subunit vaccines trigger an immune response that nearly everyone can withstand.

To securely deliver the viral pieces that constitute a subunit vaccine, scientists purify protein compounds and insert them into a harmless virus, one destined not to survive a perilous journey through the human body. Such viruses, known as viral vectors, were used to create the Ebola vaccine. In the case of the novel coronavirus, for instance, the adenovirus vector would be an apt choice.

For many years biotech companies have tried unsuccessfully to produce genetic vaccines, which use genetic code in lieu of the actual virus or its individual parts.

One prominent COVID-19 vaccine candidate is based on RNA, which the virus uses as its genetic code; it is unproven as yet. Because we are in the area of the unknown, we do not know which vaccine type will work—and the best strategy is to try them all, mounting a massive effort that is fortunately already underway.

WHY VACCINE DEVELOPMENT TAKES SO LONG

Why does Anthony Fauci, director of the National Institute

Why does Anthony Fauci say it could take 18 months to produce a safe, fully functioning vaccine? The difficulty is finding a vaccine that works against a very particular disease on the one hand and for all of humanity on the other.

of Allergy and Infectious Diseases, say it could take 18 months to produce a safe, fully functioning vaccine? The difficulty is finding a vaccine that works against a very particular disease on the one hand and for all of humanity on the other. This is why vaccine development normally proceeds at a glacial pace compared with that of other pharmaceuticals—not for lack of trying or innovation but because safety must be proved beyond a shadow of a doubt.

Therapeutic drugs are generally prescribed to sick people as needed; vaccines are generally given to healthy people en masse. It takes a couple of days for scientists administering experimental treatments to hospitalized coronavirus patients to determine their safety and efficacy; for those injecting vaccines into as yet unaffected test subjects, it could be years. Add the multipronged challenge of manufacturing and distributing a packaged good in a volatile global marketplace, factor in the estimated hundreds of millions of dollars in expenses, and voilà—you will see why many experts doubt that we will have a COVID-19 vaccine as early as this fall.

We know that some antibody responses can actually make a disease worse. This proved to be the case most recently for the dengue virus in the Philippines, and there is some hint that issues of this kind will arise with

the novel coronavirus. If a vaccine is to be administered to a sizable portion of the human population, it falls on us to proceed with the utmost caution. We must still move as fast as we can with as many resources as we can, but we must do so carefully—or risk exacerbating the spread of the current pandemic.

We need to rigorously test the dozens of vaccine candidates in the running to find one that works, and that will take some serious funding. On average, it may cost \$25,000 or more per participant to put a vaccine through clinical trials. It may also take tens of thousands of participants to ensure that a vaccine candidate is effective and safe. That means it would cost upward of \$250 million just to recruit people for a single vaccine candidate. Multiply that \$250 million by 10—the minimum number of vaccines, in my view, that must reach this stage—and add that amount to the costs of research and of developing a manufacturing process, and the sum total could be somewhere in the neighborhood of \$10 billion.

Even \$10 billion would be a low price to pay for developing a means to stop a pandemic that is paralyzing economies around the world. No matter how much money it takes to develop a viable vaccine, it will be worth it. We can't afford not to.

Medical Euthanasia Brings New Questions for Researchers

Some individuals choosing physician-assisted death donate their tissue to science

By Colin Barras



IN 2016 CANADA BECAME ONE OF THE FEW COUNTRIES IN THE WORLD TO legalize voluntary euthanasia. Since the passage of the new rules, people living there with a “grievous and irremediable medical condition” can choose to have their lives ended by the administration of a lethal cocktail of drugs. Many medical organizations, including the World Medical Association, are strongly opposed to the practice. But now a further ethical dilemma has emerged: some of the patients seeking physician-assisted death have also expressed their wishes to donate their tissues to science to help researchers treat and cure their illnesses in future generations.

Already several people with advanced multiple sclerosis (MS) have volunteered to donate brain samples to medical research after undergoing voluntary euthanasia—known formally in Canada as medical assistance in dying. Their tissues have been collected within an hour of their death, a meaningfully short window of time for gathering brain samples, according to researchers: “With a long delay between death and autopsy, the tissue degrades,” says Alexandre Prat, a neuroscientist at the University of Montreal. This makes it almost impossible to establish the activity of genes and proteins inside the brain lesions associated with MS. With what Prat terms “ultra-fresh” brain samples collected shortly after death, researchers can access this information. Doing so, he says, might shed light on the underpinnings of disease and, ultimately, lead to improved treatments.

Whereas the potential scientific benefits are clear, the ethics of the practice are muddier, and they have implications for the patient, their loved ones—and the global medical community.

Research into conditions such as MS has traditionally been made easier by the use of animal models of disease. More recently, three-dimensional brain “organoids” have emerged as a promising new tool for researching MS. But there is no substitute for the kinds of insight made possible by studying tissue samples collected from people with the condition.

“It’s all well and good to say: We saw this biologic response or mechanism of action in a rat model and we assume these are probably relevant in humans,” says Brian Kwon, a neuroscientist and spine surgeon at the University of British Columbia. “It’s quite another thing to have an opportunity to test those assumptions in human patients.”

But collecting brain samples from people with conditions such as MS is challenging, Prat says. The brain does not heal well, which prohibits researchers from taking biopsies from those living with the condition, he says. This means brain samples must be collected after death. There is anecdotal evidence that some people

with MS are eager to donate their brains for research. For instance, when the subject was raised in a 2017 article written for the digital publication *Multiple Sclerosis News Today*, several people with MS left comments below the story expressing an interest in donating their own brains. “I didn’t think MS patients were allowed to donate organs,” wrote one commenter. “I would like to donate my MS brain to help in MS research.”

But if there is a significant delay between the declaration of death and sample collection, the tissue loses its medical value, Prat says. Wait just five or six hours between death and the postmortem examination, and it is only stable proteins that will remain detectable in the samples, he says. “Unstable proteins will be degraded, and RNA will be useless. It’s a really big limitation in terms of what we can study at the pathological level.”

After Canada’s new laws allowing assisted dying went into effect, Prat and his colleagues approached a few patients with MS who had elected to undergo medical euthanasia and asked whether they would also consider donating brain samples for research. The way Canada’s laws are written means that people with serious but nonterminal conditions such as MS may qualify for medical euthanasia if their health status is so poor that death is considered “reasonably foreseeable.” Moreover, slightly under half of the people who undergo assisted dying in Canada do so in a hospital setting, which means a postmortem team can be put on standby in a nearby autopsy room to collect tissue shortly after death is declared.

So far about half a dozen people who have undergone assisted dying have agreed to donate their tissue to the research led by Prat, he says. Loved ones can remain with the patient for up to an hour after death is declared for any final goodbyes, then the body is transferred to the autopsy room. The person's brain is removed, and MS-associated lesions are sampled. Some of those samples remain at Prat's institution; others are immediately shipped to his collaborators as far away as the U.S. and France. Prat says the teams are using a technique called single-cell RNA-seq to work out the quantity of different forms of RNA in the samples. They also use immunohistology to characterize the tissue within different brain lesions and use flow cytometry to identify particular cell types.

According to Prat, MS is such a heterogeneous disease that there is real value in establishing the exact cellular and molecular features of individual brain lesions. "In MS the brain has hundreds or thousands of lesions, and each lesion is different," he says. The data he and his colleagues are collecting will go toward building a database that explores the limits of that variation. It could ultimately lead to better treatment options for MS tailored to the individual patient.

"The shorter the postmortem delay, the better the quality of the brain tissue," says Inge Huitinga, a neuroscientist at the Netherlands Institute for Neuroscience in Amsterdam. "Short postmortem delays allow state-of-the-art analyses of the tissue."

Huitinga is director of the Netherlands Brain Bank, which has, since the mid-1980s, accepted autopsy samples from donors with a range of neurological and psychiatric disorders, as well as from people who had healthy brains at their death.

A small number of the brains in the Netherlands Brain Bank came from donors who underwent euthanasia, which has been legal in the Netherlands since 2002.

Huitinga says, however, that in her experience there is little qualitative difference between these brains and those donated by people who died in other ways. One reason is that more than 80 percent of those who qualify for euthanasia in the Netherlands choose to undergo the procedure at home. This means that even though the time and date of death can be established in advance, there is still a delay while the body is transported to the hospital before the postmortem examination can begin. "In the end, the average postmortem delay does not decrease due to medically assisted death in the Netherlands," she says.

ETHICAL CONSIDERATIONS

Consequently, Prat's research appears to be unique. Because half of the people undergoing voluntary euthanasia in Canada do so in a hospital, that country may be the only place where it is often possible to collect brain tissue samples within an hour of the declaration of death. Trevor Stammers, a bioethicist at St. Mary's University in London, who studies the ethics surrounding euthanasia and assisted suicide, is unaware of anyone collecting samples for research in the way Prat and his colleagues are. But Stammers says that Prat's work raises some familiar ethical questions because in a few countries it is already possible to donate organs (principally the liver and kidneys) for transplant following voluntary euthanasia.

Such procedures have been performed in Belgium and the Netherlands for about a decade, and they are now being performed in Canada. Dirk van Raemdonck, a thoracic surgeon at University Hospitals Leuven in Belgium, says organ donation is made possible because the cocktail of barbiturates, morphine and paralyzing agents used to induce death does not appear to have toxic effects on the organs harvested for donation.

Again, there is a need to begin the autopsy as soon as

possible after death so that organs can be collected before they degrade—although in this case there is not quite the same level of urgency as that connected with brain-tissue collection, and a delay of a couple of hours is generally deemed acceptable, van Raemdonck says. But Stammers says even this slightly reduced sense of medical urgency following euthanasia risks disturbing the relatives' grieving process. He suggests that it could even lead to later uncertainty that their loved one is actually dead if the body is removed before they have had time to be sure for themselves.

Prat's experience of brain-tissue collection from people with MS suggests that this is not the case. Family members are told they can have about 60 minutes alone with their loved one after death has been declared, so they can achieve closure, but he says many choose to waive that right so that the autopsy can begin sooner.

Stammers, however, wonders whether family members are truly at peace about this process. He suspects that some may worry about letting the doctors down by spending too much time with the body and jeopardizing the medical value of the tissues or organs.

Andreas Rudkjøbing, chair of the Medical Ethics Committee at the World Medical Association and president of the Danish Medical Association, raises another concern. It is always stressed to those who apply for euthanasia that they can, at any time, withdraw their request. But if candidates for euthanasia then also agree to donate tissue to medical research following their death, they may feel they have lost the option to decline going through with euthanasia, again because they worry about letting down the doctors. "It will be harder for the patient to change his or her mind if he or she has promised to participate in research," he says.

It may be too early to say whether these concerns play out in the real world.

But performing MS research on samples obtained from

people who have undergone assisted dying raises other ethical complexities. In principle, the research Prat and his collaborators perform could lead to new therapies for MS that benefit people the world over, including those in countries in which voluntary euthanasia is still illegal and might even be considered unethical.

“I think it is worrying,” Rudkjøbing says. “The World Medical Association is firmly opposed to euthanasia, and we would be similarly opposed to using the practice of euthanasia to facilitate clinical research.”

Dominic Wilkinson, a medical ethicist at the University of Oxford, takes a different view. He argues that knowledge does not have ethical value in itself. Some researchers might feel uncomfortable about performing research on cell lines obtained from people who have opted for voluntary euthanasia. But Wilkinson says it makes less ethical sense for the researchers to ignore knowledge that others have gained by studying such tissue.

Perhaps the most important concern to bear in mind is how research such as Prat’s is perceived by the general public. There are huge benefits to be had if people are willing to donate their tissues and organs after death—whether that death be natural, accidental or medically assisted. But people may be prepared to become donors only if they feel they can trust the donation process. Stammers fears that if discussions surrounding donation become muddled with discussions around the controversial issue of voluntary euthanasia, some people who would otherwise consider donating tissues for research may decide not to.

“I’m very pro-organ and tissue donation,” Stammers says. “Hence my concern about anything that might jeopardize it and harm the trust that is essential for it to work.”

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● *Opinion*

BEHAVIOR & SOCIETY

The True Costs of the COVID-19 Pandemic

It will kill many directly, but the effort to fight it will incur a huge toll on other aspects of our health and well-being

COVID-19 has swept the world in a global pandemic of extraordinary proportions. The debate about its eventual health costs continues to rage, but one estimate from the Centers for Disease Control and Prevention suggested that anywhere between 200,000 and 1.7 million deaths could be expected in the U.S. alone, depending on the eventual fatality rate and not adjusting for corrective measures currently in place. (As of publication time, total U.S. deaths have surpassed 60,000, as reported by the Institute for Health Metrics and Evaluation.) This makes the pandemic a terrifying proposition—one that has appropriately galvanized public attention globally.

In direct response, countries worldwide, starting with China, where the virus was first diagnosed, have been implementing physical distancing measures that are becoming increasingly



comprehensive and prescriptive as COVID-19 infections continue to rise and threaten to overwhelm health systems. These measures vary by state and locality in the U.S., and by early April they included 30 statewide orders generally directing people to stay at home except for essential activities.

There is little question that some of these measures are necessary and that absent such efforts we run the risk of overwhelming fragile health

care systems and incurring substantial mortality. The challenge, unfortunately, is that the solution we are adopting is not cost-free and can have devastating health consequences in and of itself. We are causing an economic slowdown of the entire country and, by consequence, the world, the effects of which will be felt for years to come. In terms of employment, the initial signs of damage are sobering. Since the pandemic began, the number of unemployment claims in the U.S. have

exceeded 30 million. Should unemployment continue toward 20 percent, as some forecasts indicate, tens of millions of Americans could be out of work.

Unlike the Great Recession, in which almost everyone was affected, it is highly likely that because of the nature of these measures, job losses will disproportionately be among lower-paid jobs where teleworking is not possible. Data from the U.S. Bureau of Labor Statistics (2017–2018) showed that only 9.2 percent of jobs with earnings equal to or below the 25th percentile could be done through telework.

Reflecting historical and structural injustices in the labor market, there are also stark differences by race and ethnicity in the ability to work remotely. Those who cannot do so include a disproportionate number of African-Americans and Hispanic/Latino-Americans; whites are twice as likely to be able to telework than are minority groups. Unemployment because of social distancing, in addition to being vast in scope, is thus likely to exacerbate existing inequities among racial/ethnic groups.

The attendant loss of income will most affect those least able to afford it. Data from 2018–2019 compiled by the U.S. Federal Reserve suggested that one in 10 U.S. adults already struggled with monthly bills. The research also reported that if faced with an unexpected bill of just \$400, 27 percent of Americans would need to borrow or sell something to pay for the expense (excluding the use of credit cards) and that 12 percent would not be able to cover the expense at all. These figures are likely to increase

in response to job losses and reductions in available working hours in these populations.

Compounding job losses is the effect of school closures. School systems provide significant social support, particularly for single-parent households. More than 10 percent of all African-American households consist of a single female parent with one or more children, now facing the double burden of job insecurity and a lack of child care options. School closures also disproportionately affect the more than 1.3 million U.S. schoolchildren who were already homeless, for whom the support of a school environment is particularly essential.

The coming economic recession is also likely to have a lasting effect on salaries in the longer term, with particular implications for those graduating in 2019–2020. Young workers often bear a significant burden in times of recession in terms of both higher unemployment rates and lower salaries, which tend to fall the most for new entrants to the job market. Just over half of graduates following the Great Recession found a job within nine months after graduation, often with poorer conditions and pay than they would have had otherwise. These consequences are long-lasting, with drops in earnings persisting decades later. Compared with those starting work amid unemployment rates of around 5 percent, those entering the job market when unemployment is high (around 20 percent) have in the past faced an average annual wage loss of 20 percent even 15 years postgraduation.

Therefore, quantifying the economic changes brought about as a result of COVID-19 will require that we account for the disproportionate

effect on the 38.1 million Americans already in poverty (a number likely to substantially increase), the almost four million college graduates in 2019–2020, the 6.6 million Americans who had filed for unemployment by early April, and the many more who may lose their jobs in the coming weeks. While the relief package enacted by Congress stands to mitigate some of these changes, much will depend on how the measures in that package are actually implemented and the extent to which the implementation succeeds in stanching job losses from economic contraction.

The scale and unequal distribution of this disruption to human life must give us pause. Such measures do not just cause economic disruption but also are acutely harmful to population health. Focusing only on the health harms associated with unemployment, loss of income, and the broad impact on mental health outcomes associated with traumatic events and social isolation can give us a sense of the tip of the iceberg.

Unemployment has long been associated with a significantly increased risk of death in general, particularly for low-skilled workers in the U.S. The risk of heart disease, the leading cause of death in the U.S. at almost 650,000 deaths a year, has been shown to increase by 15 to 30 percent in men unemployed for more than 90 days. Among older workers, involuntary job loss can more than double the risk of stroke, which already claims 150,000 lives in the U.S. every year, as well as increase the likelihood of depressive symptoms that then persist for years. Such harms are likely exacerbated by concomitant longer-term social isola-

tion, which itself is associated with a 30 percent increase in mortality risk. Loneliness and social isolation have been associated with a 29 percent increase in the risk of incident coronary heart disease and a 32 percent increase in the risk of stroke. The scale of these elevated health risks is significant—comparable to that caused by taking up light smoking or becoming obese.

Income itself, of course, is strongly associated with poorer health across the income distribution, whether measured by life expectancy, health status or infant mortality. The gap in life expectancy between the richest and poorest 1 percent of individuals in the U.S. is around 14 years, a gap that, unlike in other high-income countries, has continued to grow in recent years.

The loss of earnings associated with being on a recessionary economic curve on graduation also leads to adverse and lasting health outcomes. Graduating in a recession is associated with a roughly 6 percent increase in that cohort's mortality rate, adjusting for age. A 1 percent increase in state unemployment level when first entering the job market has been associated with a 6.7 percent increase in depressive symptoms among men by age 40.

The toll on mental health at the population level is also likely to be substantial, bearing in mind the combination of social isolation, job and income loss, and justified fears regarding COVID-19. Previous research has shown severe economic recession to be associated with an increased prevalence of psychological distress, common mental disorders, substance use disorders and suicide.

The unemployed, those in debt or facing financial

difficulties, people with preexisting mental health problems, and families with children are particularly affected. Economic recession is in itself a traumatic event, particularly when combined with a pandemic and social distancing measures. Following other natural or human-made disasters, the prevalence of post-traumatic stress disorder has been reported as 30 to 40 percent among those immediately affected, 10 to 20 percent among rescue workers and 5 to 10 percent in the general public. Almost 10 percent of New Yorkers increased smoking rates, and almost 25 percent increased alcohol intake after the September 11 terrorist attacks.

COVID-19 is a global health threat that demands bold action, despite gaps in our data and understanding. Yet all actions we take need to account for the full scope of their consequences, particularly as those consequences pertain to the most vulnerable in society. Serving the public good requires that we recognize the urgent threat COVID-19 represents while bearing witness to the inequity this crisis and measures to address it are exposing and exacerbating.

It also demands that we treat both with the same attention. The public discussion around COVID-19 has seen much conversation about the consequences of the urgent—those affected by the virus itself—but far less conversation about the important consequences of our mitigation efforts. Both are essential, both shape the health of the public, and both need to inform public policy, including our present-day actions and our future thinking about how we prevent the consequences of pandemics to come.

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 **Opinion**

PUBLIC HEALTH

A New Web Tool Can Help You Figure Out If Those Symptoms Might Be COVID-19

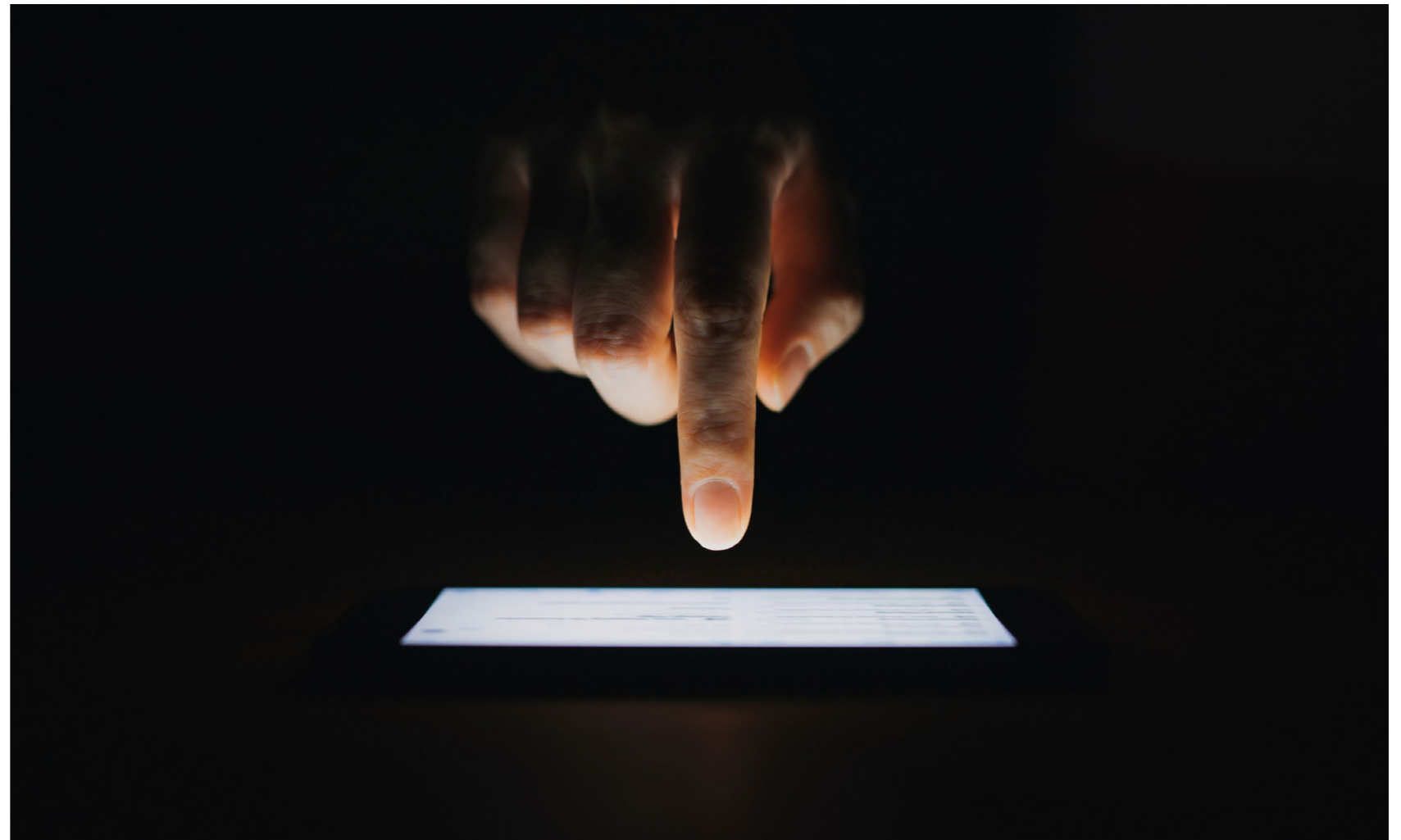
It is not meant to diagnose, but it can flag signs and risk factors that indicate the possibility of serious disease

On March 12, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. A pandemic occurs when a new disease for which people have no immunity spreads across the globe, being readily transmitted from person to person. In the past century we have had four pandemics, all caused by novel strains of flu, the worst being the pandemic of 1918, in which a third of the world's population became ill and about 675,000 people in the U.S. died. The most recent flu pandemic occurred in 2009. In contrast to previous pandemics, it was considered mild. Yet the U.S. Centers for Disease Control and Prevention recorded more than

60 million cases in the U.S., including 274,000 hospitalizations and over 12,000 deaths.

On March 26, 2020, the Institute of Health Metrics and Evaluation, a group committed to helping policymakers and donors determine how best to help people live longer and healthier lives, presented its first set of estimates predicting the use of health services for COVID-19. It estimated more demand for hospital services than there is

capacity to deliver. Health systems prepared for weeks in anticipation of a tsunami of patients. Through public health policies aimed at keeping us physically separated (or socially distanced), the acceleration of the outbreak and the total number of people sick at any given point in time can be reduced. Hospitals will make more space for patients by decreasing non-COVID-related hospital utilization through cancellation of



elective surgeries and by setting up tents in their parking lots.

It will also be important to reserve hospital resources for those who need it most. If millions rush to the emergency department to get answers about their COVID-19 symptoms, it not only will make it harder for patients with time-critical conditions to access care, but it also could fuel the pandemic by causing people sick with COVID-19 and patients at risk of catching it to spend hours together in crowded waiting rooms.

In 2008 Emory University convened a group of experts to devise a strategy to assess huge numbers of patients during a hypothetical flu pandemic. Its goal was to develop a tool that could identify persons in greatest need of hospital services. The product of their deliberations was SORT, or “Strategy for Off-Site Rapid Triage.” SORT employs a three-stage process: the first stage asks for the person’s signs and symptoms of illness, the second helps to determine whether the person is having a medical emergency, and the third inquires whether the individual has underlying medical conditions that could put him or her at risk for more serious disease.

Based on this assessment, persons are identified as “high risk” and referred immediately for emergency care, as “intermediate risk” and advised to seek timely evaluation by a health care provider, or as “low risk” suited for recuperation at home. Using this tool, people are educated about their health condition, thereby decreasing the demand for hospital services without discouraging appropriate use. The tool was rapidly adapted

for the 2009 H1N1 flu pandemic for use by nurse advice call lines and through an interactive Web site. After rapid validation, as well a review and endorsement by government agencies and professional associations, the SORT self-evaluation application was hosted on the Department of Health and Human Services’ flu.gov Web site, as well as on the Microsoft Corporation’s H1N1 Response Center. The sites had over two million hits and more than 670,000 completed self-evaluations in a little over two months.

Recently, with a surge of patients expected because of COVID-19, Emory, together with technology partner Vital, convened experts in infectious disease, emergency medicine, health literacy and public health to adapt the SORT tool for the new pandemic and created C19check.com, a Web-based, public-facing, consumer-grade, COVID-19-specific self-assessment platform.

The tool is not diagnostic and is not a replacement for evaluation by a health care provider; rather it helps the general public better understand their signs, symptoms and risk factors for more serious disease, and it directs them to the CDC guidance that best serves their needs. The tool also helps the public use this guidance as they consider how best to seek evaluation and care. It is free to the public, collects no personally identifiable health information and can be used daily to register any changes you might have in symptoms. It can even alert you to reassess yourself if you desire.

In the first three days after C19check.com launched, it had more than 600,000 hits and was

accessed in 20 different countries. It has been translated into Spanish, Portuguese, Italian, German and many other languages. A “white label” option allows an organization to assign a custom output language, creating opportunities to direct people using the tool to additional personalized health assessment options, such as connection with a telehealth provider, a nurse advice call line or a local health department hotline. Its underpinning, the original SORT algorithm, has since been widely emulated, as demonstrated by the CDC, Apple and many health organizations deploying similar symptom checkers.

These tools serve to educate the public about their illness, advise those with medical emergencies to get help immediately and, when appropriate, steer individuals away from crowded hospital and office waiting rooms, helping to maintain social distancing and to reduce inadvertent disease transmission in crowded spaces. Creating an opportunity for data aggregation, they can also help identify hotspots of COVID-19 activity and can provide estimates of the number of affected persons with underlying medical conditions and of those being directed to seek emergency care.

Much will need to be done in the coming weeks and months for our communities to be best prepared to meet the challenges of this alarming pandemic. Tools that help to educate the public, direct them to credible information sources, address demands for health system resources, and further facilitate social distancing will play an important role in our fight to beat the pandemic.

Paul Shapiro is author of *Clean Meat: How Growing Meat without Animals Will Revolutionize Dinner and the World* and is CEO of The Better Meat Co.

● *Opinion*

BEHAVIOR & SOCIETY

One Root Cause of Pandemics Few People Think About

It's our seemingly insatiable desire to eat meat

It is easy for those of us in the Western world to shake our heads at the live wildlife markets in China that appear to be the origin of the coronavirus pandemic now paralyzing the globe. Easy, that is, because such a practice is literally quite foreign to us. (In its defense, at least, China has now banned such markets.)

But what is more difficult is to be honest with ourselves about the kinds of pandemics we may be brewing through our own risky animal-use practices. And while the new coronavirus, crippling as it is, might have a somewhat merciful case fatality rate (the proportion of those infected who die) of less than 1 percent, we know this catastrophe may be just a dress rehearsal for an even more serious disease that could take a more gruesome toll—akin to the 1918 global flu pandemic, which originated in Kansas and killed at least 50 million people.



When that day comes, it is very likely that such a virus will also have its origin in humanity's seemingly insatiable desire to eat animals, whether wild or domestic. The conditions in which we often farm animals today—crowding tens of thousands of animals wing-to-wing or snout-to-snout—serve as “amplifiers” for viral pandemics.

Indeed, the H1N1 swine flu outbreak of 2009 appears to have originated in a pig-confinement operation in North Carolina. And while the H5N1 bird flu outbreak in 1997 evidently originated in Chinese chicken farms (its case fatality rate was 60 percent), a similar bird flu in the U.S. just five years ago led American poultry farmers to kill tens of millions of their birds to contain the outbreak, which thankfully never made the jump into the human population. And just recently both India and China announced bird flu outbreaks among their chicken factories. Similarly, these flu viruses are not yet affecting human health.

But you can play viral Russian roulette for only so long, which is why public health experts concerned about zoonotic diseases have for years been ringing the alarm about the industrial farming of animals. Michael Greger, author of *Bird Flu: A Virus of Our Own Hatching*, calls factory farming a “perfect storm environment” for infectious diseases. “If you actually want to create global pandemics,” he warns, “then build factory farms.”

In fact, in 2007 an editorial on the topic was published in the *American Journal of Public Health*, noting that our mass-raising and slaughtering of animals for food could be the genesis of the next big global pandemic. Given the connection between

“It is curious, therefore, that changing the way humans treat animals—most basically, ceasing to eat them or, at the very least, radically limiting the quantity of them that are eaten—is largely off the radar as a significant preventive measure.”

—*David Benatar*

industrial animal agriculture and pandemic risk, the author, David Benatar of the University of Cape Town, observed: “It is curious, therefore, that changing the way humans treat animals—most basically, ceasing to eat them or, at the very least, radically limiting the quantity of them that are eaten—is largely off the radar as a significant preventive measure.”

In 2007 such a prescription might have seemed off the radar, as it would have appeared simply too unrealistic. Today, however, technological progress has made it easier to imagine taking public health experts' advice more seriously.

Yes, we humans may crave meat, but our conception of “meat” is now becoming far more diverse than in the past. Whereas “protein” was once synonymous with a hunk of flesh from a once-living animal's body, today many Americans are embracing a type of protein diversity that celebrates meat from a variety of sources.

There is the success of plant-based meat alternatives, for example, which are now a popular part of fast-food chains' menus across the country. Many forward-thinking meat companies have released their own plant-based meat-alternative offerings, too. Other smart meat companies are starting to blend plant proteins into their animal proteins, offering hybrid products that are better for the planet and for public health.

And then there is the “cultivated meat” field, where start-ups, often backed by major meat companies, are growing real animal meat from animal cells rather than taking it from slaughtered animals. This kind of meat is not yet on the market, but already many people—including this writer—have enjoyed it, and the federal government is preparing a pathway to commercialization.

Diversifying our methods of meat production not only would offer us a chance to reduce pandemic risk by cutting down the number of live animals we must raise for food but also could help mitigate numerous other risks as well. Whether the concern is climate change, antibiotic resistance, deforestation, animal welfare or something else, the benefits of broadening our protein portfolio are manifold.

As we hunker down and weather the coronavirus storm now hitting the world, let us take some of our downtime to contemplate that we have the power to reduce the chance of the next pandemic. Yes, we should curb wildlife markets, but let's not stop there. If we have the will to shut down our entire society for weeks on end, surely we have the will to slightly change our diets.

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MENTAL HEALTH

COVID-19 Is Likely to Lead to an Increase in Suicides

The psychosocial repercussions of this crisis could make the tragedy even worse

Of all the literary masterpieces describing humanity's experience of disease pandemics, none describes suicide more vividly than Ovid's *Metamorphoses*, where in response to the psychosocial distress of the plague citizens "hanged themselves, to kill the fears of death by death's own hand." Just as a pandemic has become a reality for the first time in more than a century, in a destructive "life imitating art imitating life" way, news of suicides linked to the COVID-19 crisis has swept the globe and sadly shows no signs of abating.

K. Balakrishna, a 50-year-old Indian father of three, may be the first suicide victim linked to the coronavirus epidemic. Panic is suspected of precipitating his death. Historically, disease pandemics have been associated with grave psychologi-



cal consequences. This should not come as a surprise. In its simple definition, "pandemic" describes the spread of a disease across a large region, but words such as "pandemic," "plague" and now "coronavirus" are not experienced in a simple way; they leave us riddled with fear, anxiety, grief and chaos. Balakrishna kept watching coronavirus-

related videos and became convinced that he had the virus and would infect his family: he was a victim of panic contagion. Panic can demoralize us and paralyze us with paranoia and fear, and these emotions in turn lead to hopelessness and desperation.

Emily Owen, a British 19-year-old, is likely the

youngest suicide victim of this epidemic. She had not been diagnosed with the virus or reported any symptoms. Rather the announcement of the lockdown and the impending isolation petrified her. The relationship between isolation and suffering is perfectly illustrated in Albert Camus's masterpiece *The Plague*. Camus's fictional account of an outbreak of the bubonic plague in the town of Oran now holds eerie similarity to reality: the gates of the city were closed, quarantines were imposed, the citizens were isolated from each other. He aptly compares the plight of the inhabitants to imprisonment: "they had been sentenced, for an unknown crime, to an indeterminate period of punishment." Uncertainty about how long these measures would last led the Oranians, just as they do us, to feel powerless in planning for the future.

The elderly are at particular risk. Following the SARS outbreak in 2003, there was a spike in suicide among older adults, which could be a harbinger of what is to come. Older adults are sensitive to loneliness and isolation, as they depend on strong social support, especially during difficult times. Social contact in the community is now at a minimum with social distancing encouraged. The elderly especially have been advised to reduce their social contact and remain homebound. The weakening of social networks disrupts normal social lives, and feelings of worthlessness emerge.

In just one day, two health care workers—Daniela Trezzi, a 34-year-old nurse in Italy, and a U.K. nurse in her 20s—took their own lives. Both were deeply traumatized by the horrors they experi-

enced on the frontline. Communities look to the paramedics, the nurses and the doctors as pillars of strength, but compassion fatigue—emotional burnout from caring for patients with bleak prognoses—is prevalent in these workers. Health care professionals are now being called on to make difficult ethical decisions about resource allocation, and once resources become scarce, they will be left with the role of simply diagnosing, with little to be done about treating. Add this emotional toll to the fear of contracting the disease and you have a level of hopelessness and defeat that can be catastrophic.

Even when the epidemic is under control and the isolation measures are lifted, the economic ripple effect will be immense. The looming economic crisis has already claimed its first suicide victim: the German state of Hesse's finance minister, Thomas Schäfer. In a note he left behind, he explained that he was deeply concerned that he would not manage to fulfill the population's huge expectations for financial aid. "You're going to have suicides by the thousands," Trump said in a Fox News town hall. At a White House briefing, he noted that "people get tremendous anxiety and depression, and you have suicides over things like this when you have terrible economies."

Yes, Trump's warning may be exaggerated, but it is nonetheless one worth considering. The economic crisis may not cause as many deaths as COVID-19, but the high rates of unemployment, poverty and homelessness will all cause the suicide risk to surge. And indeed, suicides tend to go up during periods of economic downturn: the sui-

cide rate rose to a record high of 21.9 per 100,000 people in 1932, in the depth of the Great Depression.

So while global attention is largely focusing on the active physical treatment of patients, populations at risk for suicide in society, now more vulnerable than ever, are being overlooked. What can be done? The government and the health care sector both have roles to play.

For example, we should immediately establish mental health initiatives focusing on educating the public and health care workers on how to best deal with the immense pressure and anxiety; this may help minimize the psychosocial toll in these times of crisis. We should also implement targeted mental health surveillance of populations at risk, including patients with a prior mental health diagnosis and the elderly, followed by effective interventions to minimize suicidal ideation. And we should proactively establish mental health programs specifically designed for the aftermath of this pandemic. The psychosocial needs of those affected will be unique, and interventions for mental rehabilitation should be designed to reflect that. Treatment should be crisis-oriented.

Above all, we must take care of one another now more than ever. In the conclusion of *The Plague*, Camus questions, through his main character, physician Bernard Rieux, whether in the aftermath of so much suffering humanity can find peace of mind. Offering a glimpse of hope, Camus concludes that we can: "if there is one thing one can always yearn for, and sometimes attain, it is human love."

Abraham Aragonés is an internal medicine physician and public health researcher at Memorial Sloan Kettering Cancer Center.

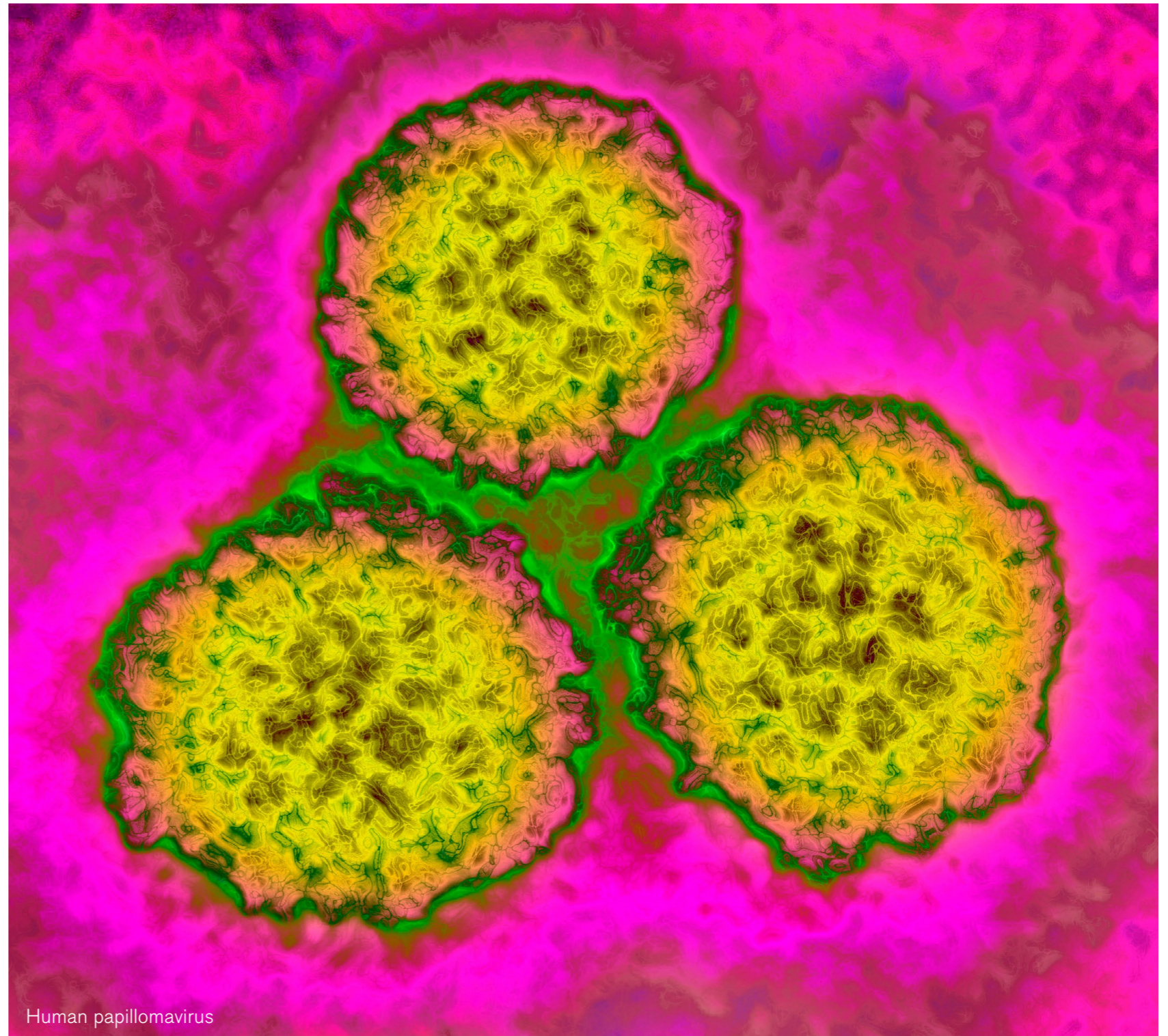
● *Opinion*

POLICY & ETHICS

The FDA and CDC Recommend the HPV Vaccine for Everyone up to Age 45, but ...

Sometimes you need to push insurance companies to pay for it

If you are in a crowded room full of adults, look to your right and to your left. The people next to you—and you, too—probably have been, or currently are, infected with the human papillomavirus (HPV). HPV is the most common sexually transmitted infection in the U.S. For most of us, our immune systems will clear the virus. But if yours fails to do so and the virus remains in your system, it can cause health problems later in life, including six different types of cancer: cervical, vaginal and vulvar cancers in women; penile cancer in men; and oropharynx (back of the throat) and anal cancers in both women and men.



Human papillomavirus

HPV is estimated to cause more than 34,000 new cases of cancer every year in the U.S., and according to the World Health Organization more than 570,000 new cases of HPV-associated cervical cancer are newly diagnosed around the world annually. Since 2006 there has been an extremely safe and effective vaccine that can prevent these HPV-related cancers.

The HPV vaccine has typically been administered to girls and boys at the age of 11 or 12 because it is most effective when administered to people at an early age and prior to exposure to the virus. The original recommendations also encouraged men and women up to age 26 to get vaccinated. More recent recommendations from the U.S. Food and Drug Administration expanded the approval of the vaccine to women and men up to 45 years of age who have not been previously vaccinated.

Following on the FDA recommendations, in June 2019 the U.S. Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) further endorsed this view and recommended that those who have not received the HPV vaccine and who fall within the new age range should speak to their providers about the potential benefits of obtaining it. For those of us who were older than the original age cutoff of 26 when the first HPV vaccine was approved in 2006, this change was welcome. But insurance companies have lagged behind the FDA and CDC recommendations, and adults between the ages of 27 and 45 years are experiencing difficulties in finding primary care provid-

Eliminating all cancer is a laudable goal, yet it is unlikely to be a realistic one. But eliminating HPV-associated cancers in a few decades is a realistic goal.

ers who administer the vaccine and in getting their insurance carriers to cover it.

ADVOCACY IN ACTION

Faced with these barriers, we took our advocacy efforts to social media. When we were first rebuffed by our health insurance company for coverage of the vaccine because of our age in November 2018, all it took was one tweet calling out the firm on social media and one follow-up e-mail for the company to revise its coverage policy for our employer. The HPV vaccine became a 100 percent covered preventive benefit for those up to age 45 who work at our cancer institute.

After this initial success, the women's group within our institution's graduate school followed up on Twitter with other insurance carriers to advocate for HPV vaccine coverage for adults, with similar success. We encourage this kind of science or citizen advocacy effort by anyone

reading this article. If all it took was a few tweets and e-mails to get coverage for our colleagues and their families at our institution, why not inquire with your own insurance providers about whether they have adopted the new ACIP guidelines for covering the HPV vaccine in people up to age 45?

Following this development, our colleagues in human resources worked with all the insurance plans offered at our institution to ensure that the HPV vaccine is fully covered not just for all who fall under the new ACIP vaccine recommendation but for anyone at any age older than nine. After reading this article, perhaps you, too, can lobby your HR partners to achieve similar coverage through your employer.

We both feel extreme gratification in knowing that we have prevented some of our colleagues from developing an HPV-related cancer, but our advocacy efforts are not simply confined to those within the biomedical realm. Publicizing the strengths and advantages of the HPV vaccine among a larger public—including neighbors, friends, family and elected officials—is a cornerstone of our work. And actively educating people about HPV and its transmission and epidemiology is just as critical as talking to them about the vaccine and its exquisite safety profile.

In fact, we are supportive of New York State Senate and Assembly bills currently under consideration that would mandate HPV vaccination for seventh graders, as well as of bills currently under consideration that would allow adolescents to consent to the vaccine without parental approval.

These kinds of decisions or policies have been enacted or passed by the local Departments of Health in Virginia, Rhode Island, Hawaii and Washington, D.C. (states and regions whose HPV-vaccination rates are among the highest in the country).

And they are under consideration in at least half a dozen other states. Public push-back has so far kept these bills from passage in New York, which might have been predicted given the strength and organization of opposition to even routine vaccination. It is time for scientists to be better prepared and more organized in their fight against misinformation and to work with colleagues, friends and family.

CONFRONTING THE ANTI-VAXXERS

The rise of antivaccination campaigns is frustrating to all of us. But there are certain aspects of the HPV vaccine that make it an easier sell. For one, remind those who say the HPV vaccine will increase promiscuity in teens that they were required to vaccinate their infants and children against hepatitis B, which is a sexually transmitted virus. Vaccination as a child did not lead to their children's early experimentation; it just preserved their livers.

This same concern has been studied for the HPV vaccine, with the exact same finding: no increase in promiscuity postvaccination. The HPV vaccine is a cancer-prevention measure, and we believe that this message should be underscored and emphasized by all of us. We encourage providers to provide a strong, unwav-

ering recommendation for this preventive vaccine to all their eligible patients.

Actively combating disinformation will be critical to the successful uptake of this vaccine and others. Concerns about the vaccine causing autism in children are overwhelmingly unsupported by scientific evidence and can be minimized, especially given that the HPV vaccine is administered to adolescents and adults. The HPV vaccine has a strong safety record, with only minor side effects related to administration of the vaccine (pain, soreness and fever). This information is provided by the CDC and FDA's Vaccine Adverse Event Reporting System (VAERS). For a further talking point, you can turn to coverage of a recent *Lancet* study that showed how safe and effective the vaccine has been. For example, in Australia, where the HPV vaccine enjoys robust uptake, cervical cancer could be eliminated in a generation.

Eliminating all cancer is a laudable goal, yet it is unlikely to be a realistic one. But eliminating HPV-associated cancers in a few decades is a realistic goal. We can hope to achieve this goal only with widespread uptake of the HPV vaccine, however. We hope that someday HPV vaccination will be a cornerstone of cancer prevention, just like mammography, skin checking and colonoscopy. Toward that goal, it is up to scientists, physicians and anyone reading this article to engage in advocacy efforts. Send those tweets and e-mails, talk to your neighbors, and vaccinate yourselves and your children. Call an elected official, spread information and combat disinformation.

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