SCIENTIFIC AMERICAN
Health & Medicine

June–July 2021

A COVID-Protected Life

WHAT THE EXPERTS SAY PEOPLE CAN DO AFTER THEY GET A VACCINE

Plus:

PLUMMETING GLOBAL FERTILITY RATES

TRUMP'S ABYSMAL PUBLIC HEALTH LEGACY

KIDS AND A COVID VACCINE

WITH COVERAGE FROM nature

LIZ TORMES

One Hurdle at a Time

Just before this issue went to press, *Scientific American* published a news story describing a new condition coined by psychologists: cave syndrome. Uniquely relevant to the COVID world, those who experience it fear leaving home and interacting as they did before the pandemic, even though they have been fully vaccinated. Several members of my close circle could easily fit this description—despite having gotten their shots, they can't imagine doing all the things they once did, like going into their friends' apartments, meeting dates unmasked or eating indoors at a restaurant.

In this collection's cover story, physician Carolyn Barber surveys the experts about how much freedom a vaccination truly confers (see "So What Can People Actually Do after Being Vaccinated?"). As she discovers, the science is young and constantly changing, giving cave syndromers a steady stream of variables and guidance to contend with.

COVID has other strange lingering effects: writer Claudia Wallis investigates the link between the disease and the onset of diabetes (see "Unraveling the Complex Link between COVID and Diabetes"). And journalist Mike May details all the other viral and bacterial threats lurking in the wings for humans to contend with (see "Tomorrow's Biggest Microbial Threats"). But for now let's all get out the door and begin healing from COVID-19 as best we can.

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Health & Medicine

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On the Cover

What the experts say people can do after they get a vaccine

WHAT'S INSIDE

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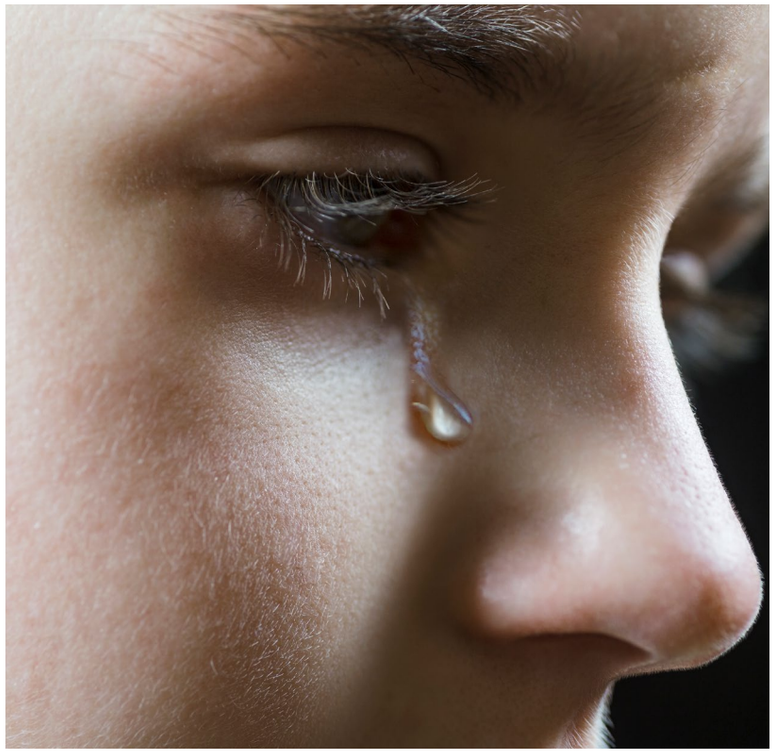

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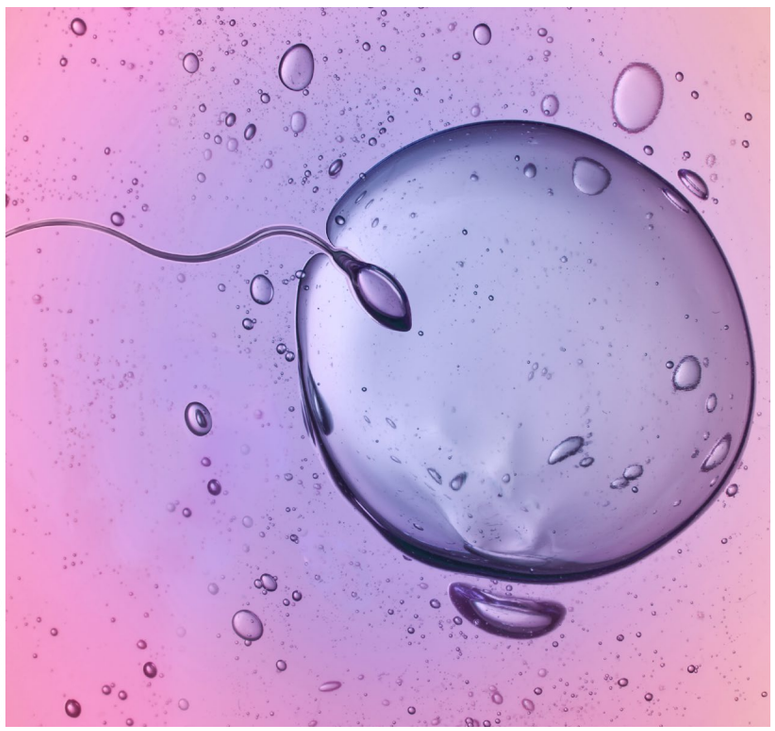

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FEATURES

OPINION

If You Don't Have COVID Vaccine Side Effects, Are You Still Protected?

Reactions reflect unique features of an individual's immune system, not the strength of a response

JASMIN MERDAN *GETTY IMAGES*

In March, Robert Duehmig and Bill Griesar—a married couple in their 50s who live in Astoria, Ore., and Portland, Ore.—were each relieved to get their second shot of the Pfizer-BioNTech vaccine for COVID-19. After the jab, Griesar felt nothing more than a sore arm. But for Duehmig, the effects were more pronounced.

"I woke up during that first night … with the chills and some body aches and just not feeling well by the morning," Duehmig says. "I really didn't want to do anything but sleep that day, which is about all I did."

The unpleasant reaction was reassuring. "I do like to think that it means it's working, that it's kicking my system into gear," Duehmig says. So was Griesar's vaccine any less effective at protecting him from severe COVID-19?

Absolutely not, according to experts and data from clinical trials of the Pfizer vaccine. The latter indicated that the vaccine was generally 90 to 100 percent effective against COVID-19 in people regardless of their sex, age, race, ethnicity or preexisting conditions. Yet only about half of trial subjects experienced the sort of systemic reactions that Duehmig did.

"The big take-home message is that not having side effects, or [having] not as severe side effects, is no reason to worry," says John Wherry, an immunologist at the University of Pennsylvania.

So why do some people get side effects and others do not? "It's a great question, and we don't know the answer," Wherry says. But ultimately the experience probably reflects the quirks of each person's immune system more than it does the vaccine's effectiveness.

"If you really feel it, you're mounting a really vigorous immune response," says Sujan Shresta, a viral immunologist at the La Jolla Institute for Immunology. "But at the same time, just because a person didn't feel anything doesn't mean the immune response wasn't vigorous. Each one of us makes a different kind of immune response." Age, sex, genetics, preexisting conditions, environment and even our diet influence how our immune systems might react, she says.

To better understand a vaccine's side effects, consider what happens when we get vaccinated. First, the innate arm of the immune system—its blunt force tool—rapidly attacks the foreign protein introduced by the vaccine, which can cause effects ranging from inflammation at the injection site to body-wide symptoms such as fatigue, pain or fever. The response activates the adaptive immune system, which takes a slower but more tactical approach: activating and training B cells, which make antibodies, and T cells, which help to coordinate future attacks. That process ultimately leads to the formation of memory B cells and T cells, which can live in the body for many months to years.

Viruses infect our cells by fitting like a key into a lock—in this case, a receptor on cells' surface. To block them, Wherry says, "antibodies act like sticking a piece of gum in the lock so the virus can't get in." Those gummy antibodies are crucial, but in order to build lasting protection, the immune system has to remember the specific shape of SARS-CoV-2, the pathogen that causes COVID-19, for its next encounter, which depends on memory B cells.

"Those cells form what we call immunological memory," Wherry says. "They stick around and form a backup system. If the antibodies fail for some reason, you still have all these other cells working."

That is why antibodies do not tell the whole story of how well an immune system is protected. For a preprint study recently posted online and not yet evaluated by outside experts, Wherry and his colleagues measured antibody and B cell levels in blood samples from 44 people receiving either the Pfizer or Moderna vaccine, taken at various times over the course of vaccination. The researchers primarily compared vaccine protection in individuals who

"If you really feel it, you're mounting a really vigorous immune response."
—Sujan Shrest

had recovered from COVID-19 with those who had never been infected. They also found, however, that people who reported systemic side effects had slightly higher levels of antibodies but not higher levels of B cells. The contrast suggests that while these individuals may have mounted a stronger inflammatory response, they were not necessarily better protected against the coronavirus in the long run, Wherry says.

Many people will feel more side effects after the second shot of a two-dose COVID-19 vaccine, providing some reassurance. That shot tends to cause more side effects because the first dose primed the body for it, Shresta says. After the first exposure, the body accumulates a finite pool of memory B cells. With the second dose, she says, "we want to expand that population for later on, so upon real infection, the immune response will be faster, bigger and better."

Wherry says that second shot may produce bigger side effects in some people because those memory B cells have already been established in response to the first exposure. "The inflammation quickly shifts [B cells] over to these antibody-producing factories," he adds.

While researchers do not fully understand why only some people have side effects from COVID-19 vaccines, epidemiological data suggest some trends. "Women tend to have more vigorous immune responses than males, and young people tend to respond more than the elderly population," Shresta says.

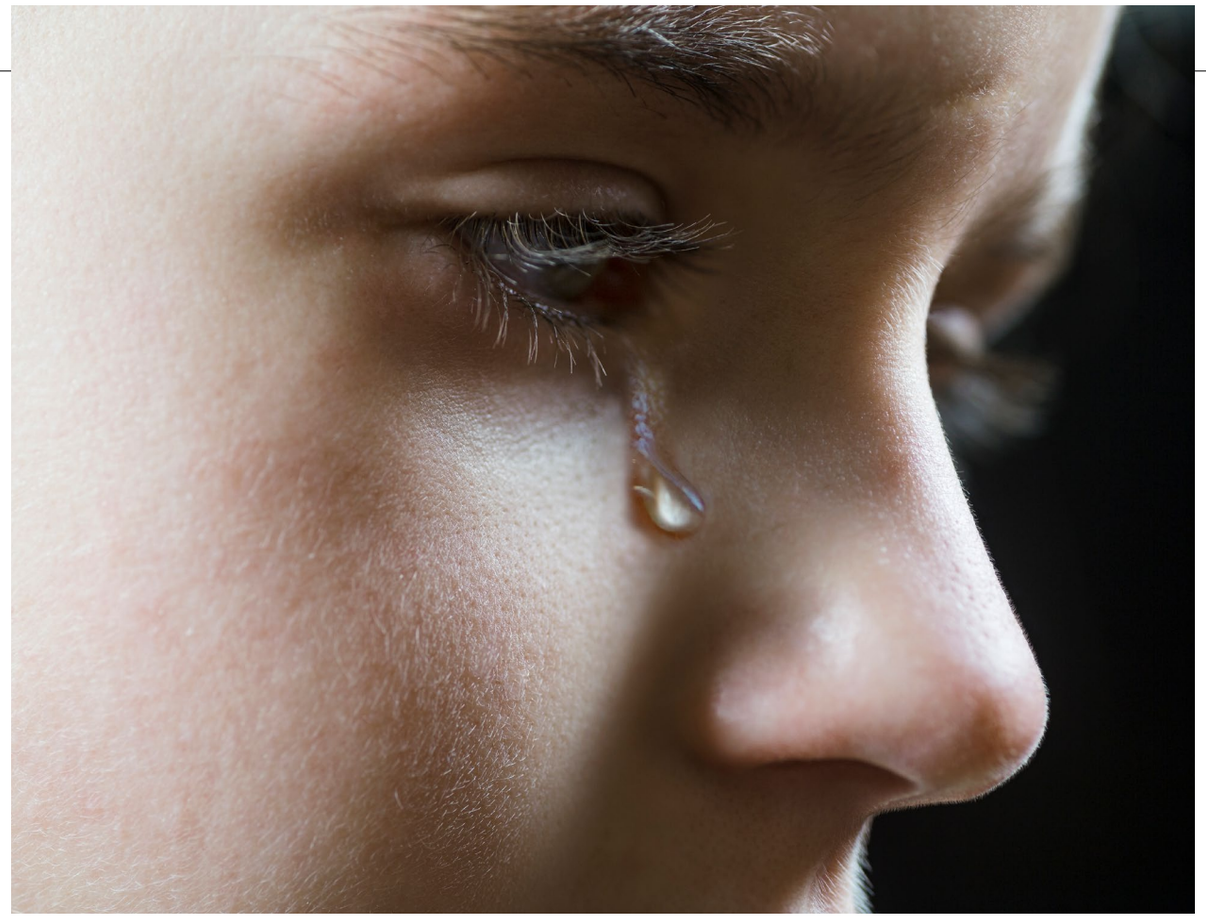
And the elderly as a whole report fewer side effects than younger people do, but that could have more to do with the way the immune system ages rather than how well the available COVID-19 vaccines work. "The efficacy in the elderly is great," Wherry says. "It reflects that these are really good vaccines [that produce] antibody levels that are 100-fold to 1,000-fold more than you need. So even in the elderly, if you lose five- or 10-fold [of that antibody

level], it's like a tree falling in the forest; it doesn't really matter."

Our individual reaction to a COVID-19 vaccine could also have to do with the coronaviruses that we encountered in the Before Times. One's immune system may have a heightened response to viruses similar to those it previously saw, whether that encounter occurred recently or decades ago. "People with young kids who get exposed to seasonal coronaviruses quite a lot may actually have some cross-reactivity that gives them more side effects," Wherry says. And, he adds, "the elderly may have seen a coronavirus 40 years ago that people in their 30s never saw before."

Although many questions remain about who gets side effects from a vaccine and why, Shresta says that the millions of people receiving similar vaccines worldwide provide researchers with a unique opportunity. "We'll really learn some fundamentals about the immune system that we can harness—not just for infectious diseases but for autoimmunity, for cancer, even for neurological diseases," she says. And that's a real shot in the arm.

—Stephani Sutherland



VLADIMIR GODNIK *GETTY IMAGES*

Scientists Grew Tiny Tear Glands in a Dish–Then Made Them Cry

Organoids made of tear-producing cells offer chances to study, and possibly treat, eye disorders

At first, it took a long time—up to a day—to make the cells cry. But, with experience and a little prodding, the researchers eventually made them weep in only half an hour.

The tearful cultures, reported in *Cell Stem Cell* on March 16, are the first tear-gland "organoids"—three-dimensional assemblages of cells that are designed to resemble miniature versions of organs. Organoids of the glands that produce tears could be used to study and eventually treat disorders that cause dry eyes, including an autoimmune condition called Sjögren's syndrome.

"It's very promising," says ocular pathologist Geeta Vemuganti of the University of Hyderabad in India.

In addition to their role in displaying emotion, tears help to lubricate and protect the eye. Dry eyes can be painful, inflamed and prone to infection.

To study tear production, developmental biologist Hans Clevers's laboratory at the University Medical Center Utrecht in the Netherlands developed a way to grow tear-gland cells as organoids. The group has found ways to grow a menagerie of organoids, including miniature livers, cervical cancers and snake venom glands.

WELLING UP

Tear glands, also called lacrimal glands, are a particular challenge to study, says Darlene Dartt, who studies tear production at Massachusetts Eye and Ear in Boston. The glands are located above each eyeball, behind the bony orbit of the eye, making them difficult to biopsy. Samples, when researchers can get them, are often tiny, she says.

Clevers's lab used its expertise to work out culturing conditions for cells from mouse and human lacrimal glands. To stimulate tear production, the team then exposed the organoids to several chemicals,

including the neurotransmitter norepinephrine, that relay messages between nerve cells and glands.

Because the organoids lack ducts, "tear" production causes them to swell. "If there had been a little duct, there would have been droplets," Clevers says. And when the team transplanted the organoids into mice, the assemblages matured and developed ductlike structures containing proteins found in tears.

The team hopes the cells can be used to study tear glands and to screen for drugs that affect tear development. Clevers and his colleagues have already used CRISPR genome editing to study tear-gland development and have found that a gene called *Pax6* is important in guiding cells to take on a tear-gland identity. *Pax6* is a known regulator of eye development: expressing the fly version of *Pax6* on the leg of a fruit fly will cause an eye to develop there.

Clevers's lab is now teaming up with Dutch naturalist and TV show host Freek Vonk to study structures resembling tear glands in crocodiles. The team hopes to use the organoids to study actual crocodile tears, which the reptiles use as a way to excrete salt.

TRANSPLANT POTENTIAL

Organoids derived from human cells could also eventually provide material for transplants, to replace diseased or damaged tear glands. Clevers's group and its collaborators have developed salivary gland organelles that will be tested in clinical trials starting this summer for people who suffer from dry mouth, a condition that can cause tooth decay and difficulty in chewing and tasting.

Those salivary-gland trials could serve as a testing ground to work out methods that could then be adapted for future tear-gland transplants, Dartt says. In the meantime, she says, the work that Clevers's team has done in characterizing tear glands—including creating a detailed cell-by-cell map of the structures and their organoids—has demonstrated that the glands are more heterogeneous than was previously appreciated and could send researchers back to reinterpret old data. "That has implications for a lot of studies."

—*Heidi Ledford*

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When Will Kids Get COVID Vaccines?

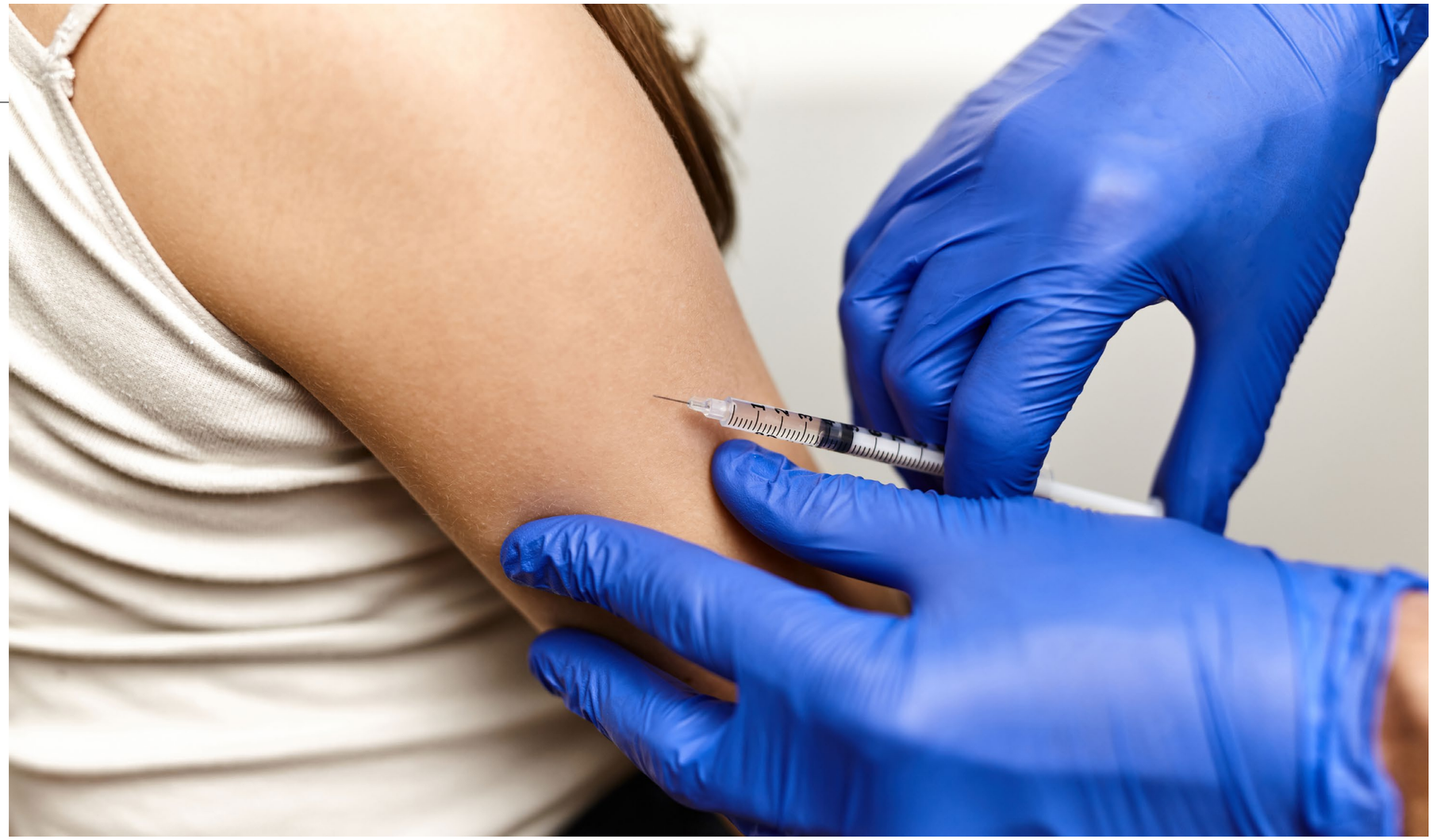
Pharmaceutical companies are starting clinical trials in young children and adolescents, but they must balance speed and safety

As adults around the world scramble to get vaccinated against COVID-19, pharmaceutical companies are turning their attention toward one quarter of the population that still has no available shots: kids.

Several pharmaceutical companies are doing clinical trials in adolescents or young children. Pfizer is already testing its vaccine in kids aged 12 to 15, and it just announced results showing that its vaccine works very well at preventing COVID in this age group. Moderna has been testing its vaccine in those aged 12 to 17. And this past March both companies began trials in children aged six months to 11 years. Johnson & Johnson recently described plans to test its vaccine in young children and adolescents, too. [*Editor's note: Pfizer announced in May that it intended to apply for FDA emergency authorization for its vaccine to be administered to children ages two to 11 beginning in September.*]

Given that most kids are at low risk for complications from COVID, the need for a pediatric vaccine for the disease may not seem pressing. But scientists say the pandemic may never be fully controlled until kids are inoculated. When we vaccinate only adults, we leave vulnerable "an enormous, immunologically naive population," says James H. Conway, a pediatrician and associate director for health sciences at the Global Health Institute at the University of Wisconsin School of Medicine and Public Health. Without a pediatric vaccine, "the disease, even if our kids don't get super sick with it, is going to be there and continue to circulate routinely."

Indeed, recent research suggests infections among kids are more common than public health authorities realized. In a Centers for Disease Control and Prevention paper published in March, researchers tested blood samples routinely collected from people younger than 18 in Mississippi between May and September 2020. Although the state had received reports of only about 9,000 COVID infections in kids through September, analyses of coronavirus



INNA VLASOVA GETTY IMAGES

antibodies in the blood suggested that roughly 114,000 of them had actually had the pathogen—meaning the virus had infected nearly 13 times more children and adolescents than the state had recorded.

The upshot of such findings is that the U.S. must inoculate kids if it ever wants to reach herd immunity. "If we think about the fact that [people] 18 and under actually make up 25 percent of the population of the United States and probably a bigger proportion of the world population, we really need to make sure that children are part of the population that are immune by vaccine," says Yvonne Maldonado, a pediatric infectious disease physician at the Stanford University School of Medicine and chair of the American Academy of Pediatrics (AAP) Committee on Infectious Diseases.

And although kids are generally at low risk for COVID complications, some are not so fortunate. More than 13,500 kids in the U.S. have been hospitalized with the disease, and 268 have died, according to AAP data released on March 18. Some of these children may have had asthma, diabetes, heart conditions, obesity, or a genetic, neurological or metabolic condition, all of which place people at increased risk for COVID complications, the CDC says. Race and ethnicity shape risk, too: according to an August 2020 CDC study, the rate of COVID-19 hospitalization is five times higher for Black children and eight times higher among Latino or Hispanic children than it is among white kids. Since last May, around 2,600 U.S. children and adolescents have also developed a rare condition called multisystem inflammatory syndrome in children, or MIS-C, weeks after having had COVID, and 33 of them have died.

It is therefore crucial to have vaccines available for kids to curb the spread of the coronavirus and to protect young people who are at high risk. But "when you're talking about putting a vaccine in children, everyone wants to make sure that it's safe," says Jennifer Nayak, a pediatric infectious disease physician at the University of Rochester Medical Center, who is helping to run one of Moderna's clinical trials in kids. This means that careful clinical trials are essential, she says. Researchers also have to take special care to minimize the risks to kids who enroll in these trials. Children do not always understand the risks involved in participating in trials, so they cannot provide informed consent, Nayak says.

This is one reason why pharmaceutical companies waited so long to begin testing their vaccines in kids. They wanted to have months' worth of data showing that the

vaccines were safe in adults first, Conway says. They also wanted to see what happened to vaccinated adults who were then exposed to the coronavirus to "make sure that if you'd been vaccinated and then got infected, that you didn't have a bizarre, enhanced immune response to the disease," which can be dangerous, he explains. This kind of reaction was, for instance, observed in some children who were vaccinated with a new dengue vaccine in the Philippines in 2016 and 2017 and then exposed to the dengue virus.

Researchers also want to be sure that the COVID vaccines do not elicit a reaction similar to MIS-C. They do not expect that result, because the immune responses seen in kids with MIS-C differ from the kinds of immune responses the vaccines elicit in adults. But they still want to be sure. "Are we particularly concerned about this? No, but it's one of the really very important reasons that the vaccines need to be studied in the pediatric population," Nayak says. As for whether kids might have more side effects from COVID vaccines than adults do, no one yet knows. "Children may have more reactions, meaning either more fever or sore arms," Maldonado says, "but they could be very similar."

To conduct the trials, researchers will first test various doses of the vaccines in small groups of kids of a particular age to determine the dose that provides protection without causing many side effects. "It's Goldilocks, essentially: this one's too hot, this one's too cold, this one's just right," Conway says. Then they will give the dose they deem best to several thousand kids and track them, along with a similar group of kids who will get a placebo shot, over time to see how likely they are to develop COVID.

The pharmaceutical companies began trials in adolescents first because they are most similar to adults. The firms are slowly turning to younger age groups. Starting with teenagers is good from a public health standpoint, too: they are more likely than younger kids to spread the virus and are also more likely to get seriously ill, Nayak says. Still, the American Academy of Pediatrics maintains that even without vaccines available for young children and teens, it can be safe to reopen schools if safety measures are taken and if community spread is limited. That recommendation was made, in part, because not having in-person school poses mental, emotional and educational risks, and when it comes to overall spread of COVID in communities, kids "don't seem to be a major driver," Conway says.

Researchers are not sure when vaccines for kids will be widely available because that will depend on the results of the clinical trials and the Food and Drug Administration's approval process. But Conway says he expects them to be ready for adolescents aged 12 to 16 this summer, for five- to 11-year-olds by early 2022, and for babies and toddlers sometime after that. Maldonado hopes the vaccine for the youngest group will also be available in early 2022.

Conway says he is pleased with how the COVID clinical trials in young people have been designed and organized in that they balance the need for both safety and speed. Children deserve to be kept safe—both in clinical trials and in the real world, where they may be exposed to the disease. "We need to advocate for kids," he says. "They deserve to be protected."

—Melinda Wenner Moyer

New Arkansas Law–and Similar Bills–Endanger Transgender Youth, Research Shows

The legislation runs counter to evidence that puberty blockers and hormone treatments are safe and save lives

This week Arkansas became the first state to ban physicians from giving hormones or puberty-delaying drugs to transgender people under age 18. Doctors who do so could be stripped of their licenses and sued. The law is called the Save Adolescents from Experimentation (SAFE) Act. It became official this past April, when the state's Republican-controlled legislature voted to override Governor Asa Hutchinson's attempted veto.

Nineteen other states have introduced similar legislation, and some of the bills outline strict penalties. Under one that passed Alabama's Senate in March, physicians who administer the treatments to minors will face up to 10 years in prison.

The state senate sponsor of the

Arkansas bill, Alan Clark, has said that puberty blockers and hormone treatments are "at best experimental and at worst a serious threat to a child's welfare." But medical and scientific organizations say his claim is wrong. They include the American Medical Association, the American Psychological Association, the American Psychiatric Association, the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry (AACAP) and the Endocrine Society. These groups represent thousands of clinicians and researchers nationwide. Among them, the AACAP recently argued that "state-based legislation regarding the treatment of transgender youth that directly oppose the evidence-based care … is a serious concern" that endangers young people.

Experts say claims that gender-affirming medical treatments are experimental or risky are flawed on several levels. Puberty blockers—a class of drugs called GnRH agonists that dampen the effects of sex hormones—have been used safely for decades to delay puberty in children who start it too early. In transgender youth, the drugs are used to prevent the development of permanent sex characteristics such as breasts and voice changes at the onset of puberty—generally age nine or older. Gender-affirming hormones—testosterone or estrogen—are not usually given until a person is in their teens. These hormones promote the development of sex characteristics that are different from those of the sex that an individual was assigned at birth.

Data are starting to emerge about the long-term effects of these treatments in young people diag-

NADIA BORMOTOVA *GETTY IMAGES*

nosed with gender dysphoria, defined as distress resulting from a difference between one's gender identity and the sex that individual was assigned at birth, from a few studies. Teams in the Netherlands and the U.S. have been following groups of transgender adolescents from the time they begin treatment. Thus far this research has found hormone treatments and puberty-blocking drugs to be safe.

Crucially, the therapies also lower the high rate of suicide attempts and mental illness among transgender youth. Such evidence suggests that withholding treatment is not an ethical option, according to Guy T'Sjoen, an endocrinologist at the University of Ghent in Belgium, who collaborates with the team in the Netherlands. "It's not doing nothing; it's very harmful," he says.

The Netherlands group was the first to study puberty blockers in transgender children. And Annelou de Vries, a child and adolescent psychiatrist at VU University Medical Center in Amsterdam, says she has not seen any major side effects in the approximately 1,500 adolescents treated at her clinic. Last June her team published a study showing that 178 transgender adolescents receiving blockers had better psychological functioning and fewer suicide attempts, compared with 272 transgender youth who did not receive early care.

That is an important result, says Joshua Safer, an endocrinologist at Mount Sinai Hospital in New York City, given that around 40 percent of transgender adolescents consider suicide, according to one nationwide survey. Delaying puberty, he says, is a cautious approach that allows physicians to slow the development of sex characteristics without giving gender-affirming hormones to young adolescents. State laws banning the practice could cost lives, Safer says. "If we actually deny care to people, they would suffer," he says. "Going after puberty blockers sounds like sabotage to me."

The U.S. research team, which is funded by the National Institutes of Health, is seeing similar outcomes. Its study, which is the largest to prospectively follow transgender youth from the onset of treatment, was launched in 2015 and has recruited nearly 400 people. About 100 of them are early adolescents who are receiving puberty blockers at the average age of 11. And more than 300 are late adolescents receiving hormone treatment at the average age of 16. In a paper published last year, the team found that youth who received treatment at an earlier age were mentally healthier than those who did not receive it until later.

"It's true, at present, there are still many things we don't know for sure. But if we have to wait until we know everything, we will never be at that point."
—Annelou de Vries

The U.S. researchers acknowledge some confounding factors in the study. Young adolescents who go on puberty blockers tend to have support from their parents, which also helps improve mental health. And it will be many years before they can see effects that do not appear until old age. Still, "everything we've looked at thus far is incredibly encouraging," says Johanna Olson-Kennedy, a pediatrician at Children's Hospital Los Angeles, who is heading part of the NIH-funded study.

As their investigation progresses, Olson-Kennedy and her colleagues are trying to get as much information as they can about how gender-affirming treatments affect the body, which will help physicians better target treatment to individuals and know what to watch for. One major medical concern about puberty blockers is their effect on bone growth. The drugs prevent the accumulation of bone mineral in growing children, which is why physicians try not to administer them to adolescents for very long. But a study by the Netherlands team found that transgender boys' bone density returned to normal within a few years. And more recently, the NIH-funded study found that transgender girls tended to have lower bone density before starting treatment, possibly because they were less physically active than cisgender boys their age.

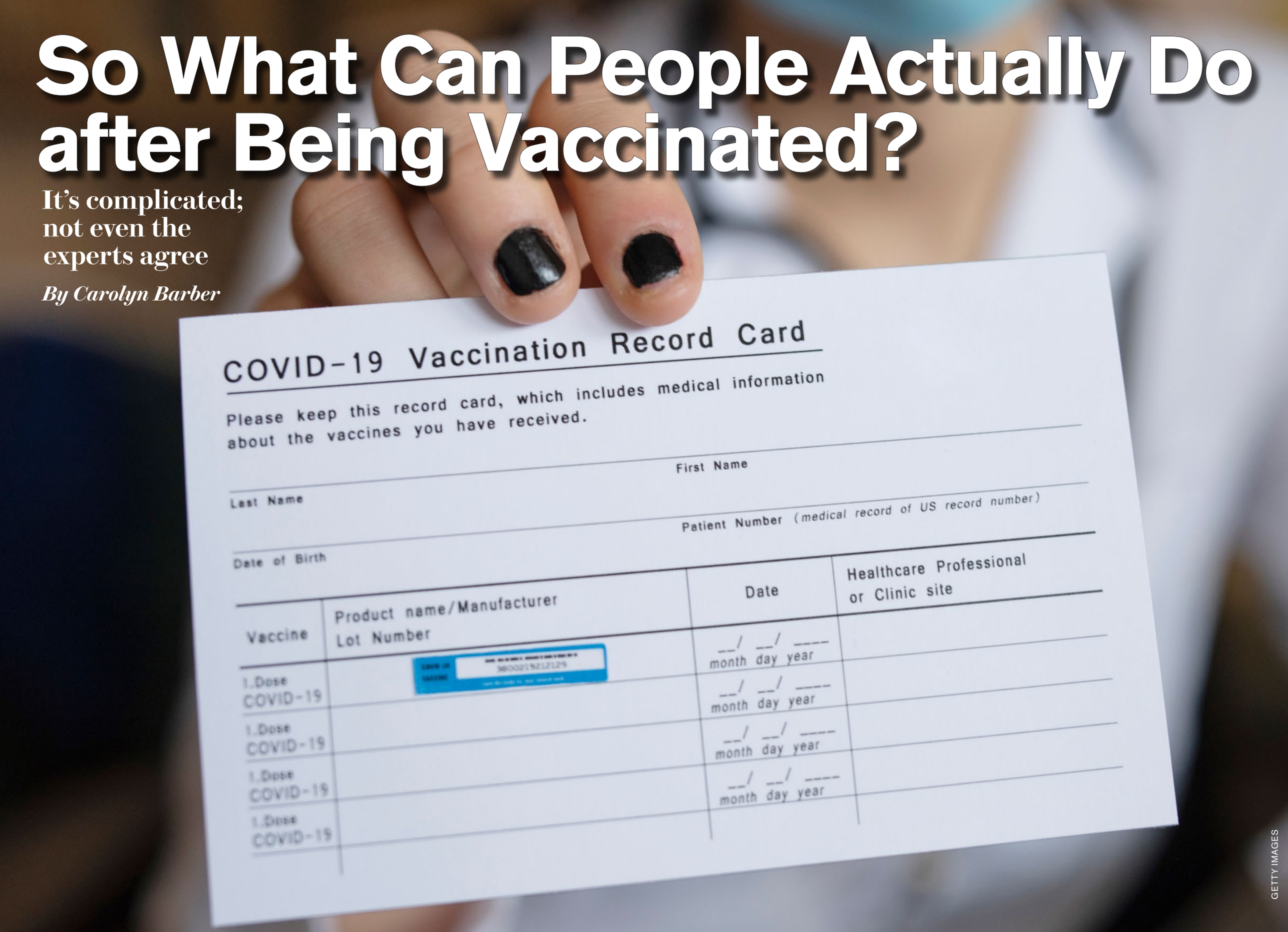
"It's true, at present, there are still many things we don't know for sure," de Vries says. "But if we have to wait until we know everything, we will never be at that point."

—Sara Reardon

So What Can People Actually Do after Being Vaccinated?

It's complicated; not even the experts agree

By Carolyn Barber



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

THE FIRST RAFT OF STORIES in the wake of the Biden administration's dramatic acceleration of the COVID-19 vaccine rollout in the U.S. centered on all the things the newly vaccinated among us can and cannot do, as if we were working off a master list of approved activities.

Like so many things associated with this pandemic, the truth is nowhere near that clean. No such list exists, and even the Centers for Disease Control and Prevention has only issued recommendations, not requirements. Community and regional medical metrics come into play, and politics will carry its own dark weight when it comes to local or statewide decisions in areas as critical as masking, capacity in buildings and restaurants, and so on.

Even such basic concepts as risk are subject to variances of opinion, as I discovered while soliciting input from several medical experts across the country and abroad. And because there are no clinical trials to address many of these questions, scientists are left to provide their best recommendations based on their interpretation of risk tolerance, both at an individual and population level, and their scientific knowledge of the virus and its kinetics.

First, here's where the experts agree: The levels of protection provided by all of the available vaccines in clinical trials were extraordinary when it came to preventing severe disease, hospitalization and death. While the new variants pose a threat, most of those interviewed believe that current vaccines should provide reasonable protection there, too.

"To date, based on the studies by Johnson & Johnson in South Africa and Brazil, the vaccines will likely prevent hospitalization and death caused by the variants," Paul Offit, an internationally recognized expert in virology and immunology and director of the Vaccine Education Center, wrote in an e-mail.

This is not the same as saying that a safe haven has been established. Most experts concurred that although we've seen declines in new daily cases of coronavirus since early January, the U.S. is still experiencing high levels of transmission of the virus, with approximately 60,000 new cases reported daily and about 1,500 deaths every day. These remain very high numbers.

"Our return to normalcy will be in two phases and is driven by two factors: the level of virus transmission in our communities and the proportion of people fully vaccinated," says William Moss, executive director of the International Vaccine Access Center and professor of infectious disease epidemiology at the Johns Hopkins Bloomberg School of Public Health. Because of the high levels of viral spread and the low proportion of U.S. citizens fully vaccinated, Moss says, things like masking, social distancing, hand washing and avoiding large crowds remain critically important.

Vaccination efforts across the country have ramped up significantly in recent weeks. Currently in the U.S., 2.1 million people are being vaccinated daily. More than 93 million doses have been administered in total, with 18 percent of Americans having received one dose and 9 percent two doses. President Joe Biden has said that coronavirus vaccine should be available to all U.S. adults by the end of May.

But the questions of mobility, interaction and risk assessment are thorny ones. The good news (and, for many, the best news) is a general consensus that vaccinated people should be able to get together with others who've also received the vaccine, ditching masks and distancing precautions. The risk of infecting one another in these so called immunity bubbles is pretty low; Anthony Fauci, the president's chief medical officer, concurs that small, maskless social gatherings in the home of those who are "doubly vaccinated" should be fine. New CDC public health recommendations for fully vaccinated people published March 8 likewise allow for fully vaccinated people to visit with other vaccinated people in a private setting, unmasked, without distancing.

Beyond that, though, the line becomes harder to draw. Monica Gandhi, an infectious disease physician and professor of medicine at the University of California, San Francisco, argues that those who've been vaccinated "are protected from severe COVID-19 infection at this point and should feel free to start engaging in activities that they miss." Those, she says, include going to an indoor bar or restaurant and attending movies, albeit with

masking and distancing protocols in place—a level of reengagement that few other experts are willing to encourage at this time. (The CDC's updated recommendations state that while the risk of going to a gym or dining indoors at a restaurant is lower for fully vaccinated people, health precautions should still be taken given the higher risk in these settings.)

Gandhi also suggested that indoor weddings, church services and school classrooms, among others, should be in play, again with masking, distancing and ventilation needs duly observed. That, for some experts, is a threshold they're reluctant to cross because of viral spread issues indoors. Paul Griffin, an infectious disease specialist at the University of Queensland in Brisbane, Australia, emphasizes the need to try to hold these larger events outside when possible, restrict anyone unwell from attending, maintain social distancing (perhaps by spacing chairs farther apart) and provide good ventilation by opening windows when possible.

If cases are running high in the community and social distancing cannot be maintained, Griffin says he would recommend mask wearing and limiting the number of attendees. Some experts go further, concurring with the CDC's latest guidance, which advise against medium- or large-sized gatherings, regardless of vaccination status. Says Moss, "The recommendations will loosen when we see further declines in cases, hospitalizations and deaths."

The experts I consulted are dealing with incomplete information, of course. We all are. And one of the things we don't yet know, but would love to learn, is how well these vaccines actually control the spread of the virus. The answer to that question may well shape the largest body of medical advice when it comes to those who've already received their shots.

While the vaccine protects an individual well from symptomatic COVID-19, we are not sure whether that person can still develop asymptomatic infection (and, theoretically, then unknowingly pass the disease on to others). "If we want to get on top of the pandemic," Griffin says, "we still need to try and reduce the chance of the virus being spread.... If a proportion of people can stay away from venues where people have a high probability of interacting, for example, people choosing takeaway food or working from home when they can, then the chance of the virus being transmitted is greatly reduced, and the effect of the vaccine rollout will be increased."

"To date, based on the studies by Johnson & Johnson in South Africa and Brazil, the vaccines will likely prevent hospitalization and death caused by the variants."
—Paul Offit

Early real-world data suggest that vaccines likely will help prevent this asymptomatic transmission of the virus, but the information is incomplete. Non-peer-reviewed data from the Israeli Health Ministry and Pfizer demonstrated an 89 percent reduction in both symptomatic and asymptomatic infections following vaccination, although some scientists believe this finding may be overstated. A vaccine trial by Johnson & Johnson, meanwhile, found that its vaccines prevented asymptomatic infection in 74 percent of recipients.

Vaccinated health-care workers in the U.K. showed an 86 percent decrease in asymptomatic infection versus those who were not vaccinated, and another preliminary study showed a fourfold reduction in viral load for infections occurring weeks after Pfizer's first vaccine, which may equate with reduced infectiousness. Moderna's vaccine data also hinted that it reduced asymptomatic infections. "It seems very likely that the vaccines in use will reduce transmission," Griffin says, "but we don't have good data on it to be able to say how much."

Gandhi is among those who believe that returning to work in person, if other co-workers have been vaccinated, is "perfectly safe." Griffin, meanwhile, cautions that even with outdoor events, "the risk is obviously not zero." The use of basic mitigating strategies, experts agreed, is going to remain front and center of any loosening of community restrictions that might result in the mixed company of those who have and have not received vaccines.

Can vaccinated grandparents travel to visit family? "Vaccinated grandparents are completely safe from severe disease with COVID-19 with the vaccines and should finally see their family again!" Gandhi says. Based on accumulating evidence showing that "vaccines prevent transmission," she says, "if there are grandchildren in the household who are not vaccinated, the grandparents will not transmit virus to them." The CDC agrees that fully vaccinated individuals (or grandparents) may gather with unvaccinated people from a single household in a private home, among those who are at "low risk for severe COVID-19 disease," without masking or distancing indoors. If unvaccinated people come from several households, then the visit should occur outdoors (or in a well-ventilated space) with proper precautions.

Why have scientists been so cautious? Gandhi believes it is partly that the vaccines themselves appear almost too good to be true. "But they are honestly that good," she added. "I think we should take the data as it comes and has been coming for vaccines reducing transmission and modify our recommendations accordingly." (Some other experts said they felt that grandparents should assess the risks versus benefits—and if they choose to travel, consid-

“It will be low case numbers, complemented with rigorous contact tracing and a high proportion of vaccinated individuals, that will eventually get us to safety—and back to normal lives.”
—William Moss

er masking and distancing until cases decline further.)

The idea of travel, particularly air travel, remains problematic. While some authorities believe that once you’ve been vaccinated, such travel is relatively low risk (assuming you maintain masking requirements), others are more cautious, suggesting that air travel should wait until greater herd immunity is achieved. At a CNN Global Town Hall, Fauci warned that vaccination should not be considered a “free pass to travel.” The CDC did not update its travel recommendations on March 8 and continue to advise that unnecessary travel be avoided.

And we don’t know about the connection between vaccination and long COVID. If those who’ve had their shots can still develop asymptomatic or mild disease, are they also susceptible to becoming one of the group known as long haulers, those who may carry the symptoms for many months after illness?

Early evidence is encouraging but slim. At Yale University, Akiko Iwasaki tweeted recently about an informal survey of 473 long-COVID patients; among those who were two weeks past their first vaccination, 27 of the respondents said their prolonged symptoms were slightly better, while 14 percent said they were slightly worse. Says Griffin, “While there is limited if any data on this (subject) to date, given the fact that we know the vaccines are not only very safe but very effective at reducing symptomatic infection and particularly severe disease, it would seem highly plausible that the longer-term manifestations or long COVID will also be reduced.”

In the end, the experts say, local conditions are going to matter tremendously. Their suggestion to the newly vaccinated: Include in your decision-making how high background rates of disease are in your community, what emerging variants may be circulating, any personal risk factors that may place you or others around you at greater risk, and the real, time-proven knowledge that vaccines are not bulletproof.

Beyond that, people will make their choices. “The only thing we can/should really do as scientists, in my opinion, is to provide people with some reasonable assessment of their risk given an exposure—but even this is very difficult to do in practice,” says Kate Grabowski, an infectious disease epidemiologist at Johns Hopkins Bloomberg School of Public Health.

We will know more in a few months when vaccine studies looking at transmission conclude and more data emerge. In the meantime, every new vaccination gets us closer to herd immunity. “It will be low case numbers, complemented with rigorous contact tracing and a high proportion of vaccinated individuals, that will eventually get us to safety—and back to normal lives,” Moss says.

Finally, a personal note: As a higher-risk individual, I found being vaccinated an incredibly liberating feeling, a weight off my shoulders. At the vaccination center where I work, every time I vaccinate someone and hand them a Jolly Rancher lollipop, we smile and celebrate a genuinely momentous occasion. The development of highly effective vaccines in less than a year is one of the most remarkable medical feats of our time. Now we just need to see it all the way through. SA

Genetic Therapies for Brain Diseases

Hopes are high for a class of drug that could treat neurodegenerative conditions–but a recent clinical trial has brought the field up short

By Diana Kwon

Evie Lewis with her parents, Elliot and Janell. Evie receives a dose of a genetic therapy every few months to treat spinal muscular atrophy.

KIM RAFF FOR *NATURE*

Diana Kwon is a freelance science journalist based in Berlin.

SUSAN

WAS STILL A CHILD WHEN SHE FIRST SUSPECTED SOMEthing might be wrong with her mother. A cup or plate would often crash to the floor by accident when her mother was serving dinner or washing up dishes. “She was, she would have said, ‘clumsy,’ but she wasn’t really clumsy,” Susan says. “Her hands had beautiful, glamorous movements, which I now recognize as early HD.”

Huntington’s disease (HD) is an inherited condition that causes widespread deterioration in the brain and disrupts thinking, behavior, emotion and movement. The disease usually begins in midlife, with subtle changes such as mood swings and difficulty in staying focused. As it progresses, people develop dementia and an inability to speak or move.

Susan, who requested that her last name be withheld to protect her privacy, vividly remembers the day she learned that her mother had the disease. It was the spring of 1982, and her mother had been admitted to a hospital because of her extreme exhaustion, frequent falls and irregular movements. There was no genetic test for the condition at the time, so she underwent a series of assessments. Her neurologist gathered the entire family into a room to break the news. “He told us that our mother had Huntington’s disease,” Susan recalls. “And that there’s no treatment and it can be wiped out in a generation if you just don’t breed.”

Those blunt words had a profound impact on the lives of Susan and her siblings: her brother decided never to get married, and her sister chose to be sterilized. For Susan, however, those options were out of reach: she was pregnant when she received the news.

Susan says that she and her husband “couldn’t decide what was the right thing to do.” One thought, in particular, was that “if we have the child, then that child will have this same decision when they grow up,” she says. “And it seemed so cruel.” Ultimately the couple made the heart-wrenching choice to terminate the pregnancy.

The gene involved in Huntington’s, called *HTT*, codes for a protein called huntingtin. The faulty version of the gene repeats a short piece of its sequence—the nucleotide combination CAG—too many times. Unlike some genetic conditions, in which a person will develop a disease only if they have two faulty copies of a gene, just one copy of the *HTT* mutation is enough to lead to Huntington’s, and carriers of the mutation have a 50 percent chance of passing it on to their children. Years after Susan’s mother passed away, the three siblings discovered that they had all inherited the disease.

There are no treatments available to stop or slow the progression of Huntington’s, even though its genetic cause has been clear since 1993. Most other neurodegenerative diseases also lack effective therapies and although their genetic roots are less clear-cut than for Huntington’s, many of the genes associated with conditions such as motor neuron disease (amyotrophic lateral sclerosis, or ALS), Alzheimer’s and Parkinson’s have been known for decades. Now the tide might be turning for treating these kinds of diseases. Many researchers are hopeful about drugs known as antisense oligonucleotides (ASOs). These are short strings of DNA or RNA letters that are designed to cling to particular sequences of RNA made by faulty genes and to rebalance the levels of proteins they produce—boosting missing proteins or quashing faulty ones.

The U.S. Food and Drug Administration approved the first ASO for a neurological disease in 2016, and there has since been an explosion of activity in this area. The field has gone from just a handful of clinical trials run over the past two decades to around a dozen currently underway for various neurodegenerative diseases—and a few have reached their final stages.

Other ASO researchers are moving beyond diseases defined by a single mutation to look at conditions with more complex genetic underpinnings. This recent prog-

ress has made many in the area optimistic about the future of the technology. Don Cleveland, a neuroscientist at the University of California, San Diego, and one of the first scientists to investigate the use of ASOs for neurological diseases, sees this as just the beginning. "There's much, much more coming," he says.

But progress in the field has not been completely smooth. At the end of March, a large phase III trial was abruptly halted because the benefit of the drug to patients did not outweigh the risks. And some researchers have long urged caution around ASOs-because their efficacy in many conditions is unknown and that the way they are delivered—often by spinal injection—is invasive.

Although the outcome of this trial was disappointing, "I don't think this is a reason for despair," says Chris Boshoff, a scientific-project manager overseeing genetic therapies at the U.S. National Institute of Neurological Disorders and Stroke. "There's still reason to be positive and enthusiastic about what this modality can accomplish."

BREAKTHROUGH FOR A RARE DISEASE

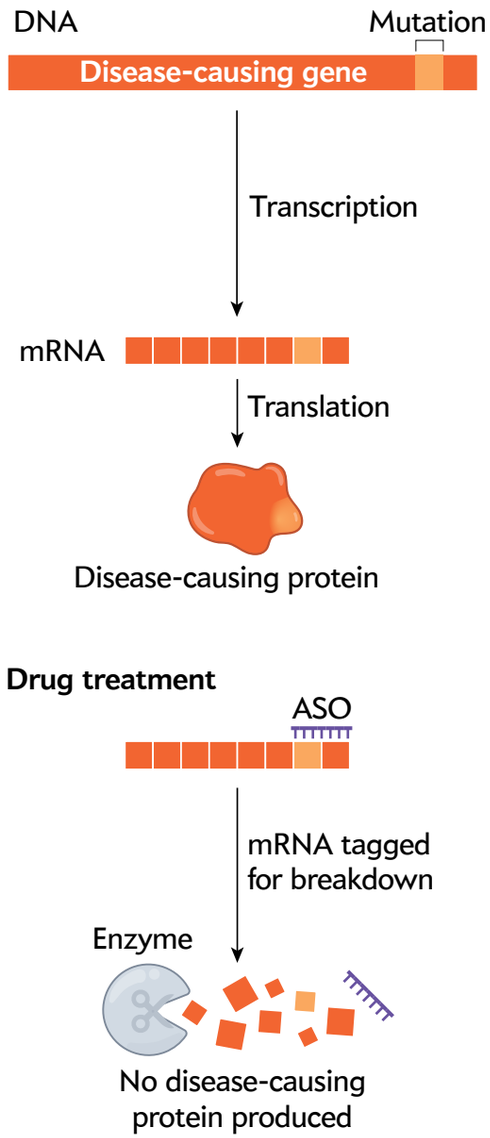
Elliot and Janell Lewis's first child, Blakely, was born in 2011 with a rare, inherited neurodegenerative disease known as spinal muscle atrophy (SMA). People with SMA have a mutated form of *SMN1*, a gene responsible for producing a protein called survival motor neuron (SMN). The resulting lack of SMN prevents the brain from being able to communicate effectively with the body, leading to muscle weakness and wasting that worsens over time. There are four types of SMA; the most common form, SMA1, is also the most severe. People with SMA1 typically show symptoms shortly after birth, and many do not survive past the age of two.

Toggling Problem Proteins

An emerging class of drug called antisense oligonucleotides (ASOs) uses tiny pieces of DNA or messenger RNA matched to disease-causing proteins to suppress or correct them.

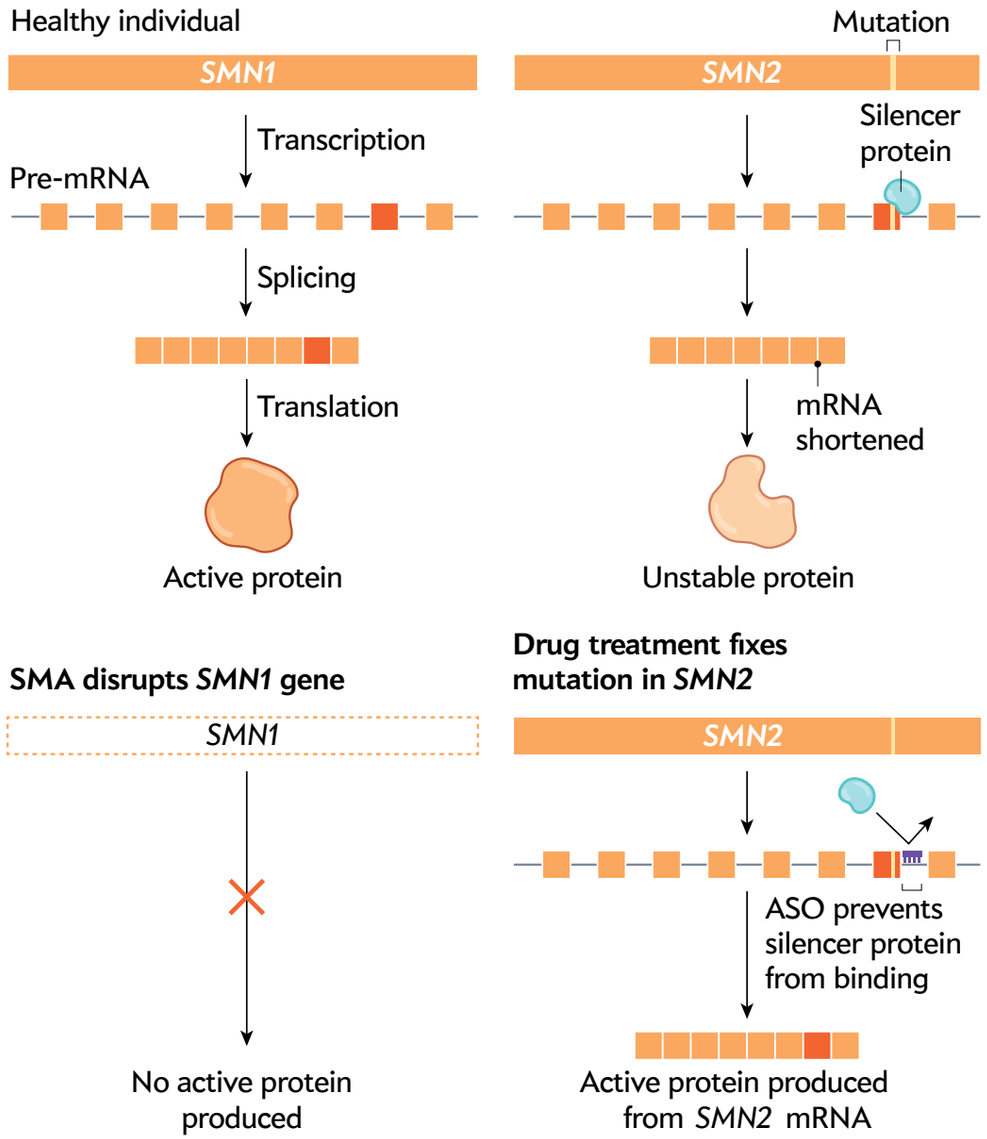
Silencing

Diseases such as Huntington's and motor neuron disease (amyotrophic lateral sclerosis) are caused by a buildup of mutant proteins. ASOs in development aim to quell their production.



Boosting

ASOs can replace missing proteins. The ASO nusinersen treats spinal muscular atrophy (SMA), in which the body lacks a protein called SMN. There are two *SMN* genes: in healthy people, *SMN1* makes a stable protein and *SMN2* an unstable version. In people with SMA, *SMN1* is disrupted. Nusinersen makes up for this by acting on *SMN2* to stabilize its normally inactive protein.



NIK SPENCER/*NATURE*

Blakely was diagnosed at three months old. “That pretty much shattered us,” Elliot says. At the time, there was no treatment, and Blakely passed away at 21 months.

In the spring of 2017, the couple had another daughter, Evie. Evie also had SMA, but she was more fortunate—a few months before she was born, the FDA approved an ASO, dubbed nusinersen, the first ever disease-modifying treatment for SMA. Evie received her first dose when she was 12 days old.

Scientists first recognized the ability of ASOs to target RNA in 1978, but it took several decades to demonstrate their clinical potential. Early on, problems such as toxicity and lack of potency stymied progress, and many drug companies lost interest. But researchers at one firm, Ionis Pharmaceuticals (originally named Isis Pharmaceuticals), based in Carlsbad, Calif., introduced key modifications to the drugs’ chemical backbone that increased potency as well as stability, enabling the ASOs to reach their targets without being degraded.

The work that led to nusinersen began around 2000 at Cold Spring Harbor Laboratory in New York, where biochemist and molecular geneticist Adrian Krainer was investigating the mechanisms that led *SMN2*, another gene that encodes SMN, to typically produce less viable protein than its counterpart, *SMN1*. They reasoned that if they could get *SMN2* to produce more protein, it could make up for *SMN1* in people with a mutation in that gene. They knew from others’ work that in almost everybody, the cause of the problem with *SMN2* was an error during splicing—the process through which strands of RNA are snipped and processed into instructions for making proteins. That causes a piece of *SMN2*’s code to be skipped.

Krainer’s team zoomed in on the proteins that bind to the RNA strand and cause the segment to be missed, hoping to stop them interfering in the process of generating complete SMN proteins. In 2004 Krainer began collaborating with Frank Bennett, a pharmacologist and one of the founding members of Ionis Pharmaceuticals. Together, they pinpointed an ASO that could bind to the strand and hide the segment from the proteins that would silence it, enabling the production of functional SMN.

Four-year-old Evie Lewis plays in the family home in Ogden, Utah.

KIM RAFF FOR *NATURE*

That compound, nusinersen, entered clinical trials in 2011. The results were so promising that the phase III trial in infants with SMA was terminated early: patients who received the drug were much more likely to meet their motor milestones and survive than were those who received a placebo.

So far more than 10,000 people worldwide have received nusinersen (Spinraza), which Ionis licensed to drugmaker Biogen, based in Cambridge, Mass., in 2016. The drug has drastically altered the course of the disease: infants with SMA who receive it shortly after birth are no longer dying within the first years of life. Nowadays “conversations [with families] don’t just end with, ‘We’re

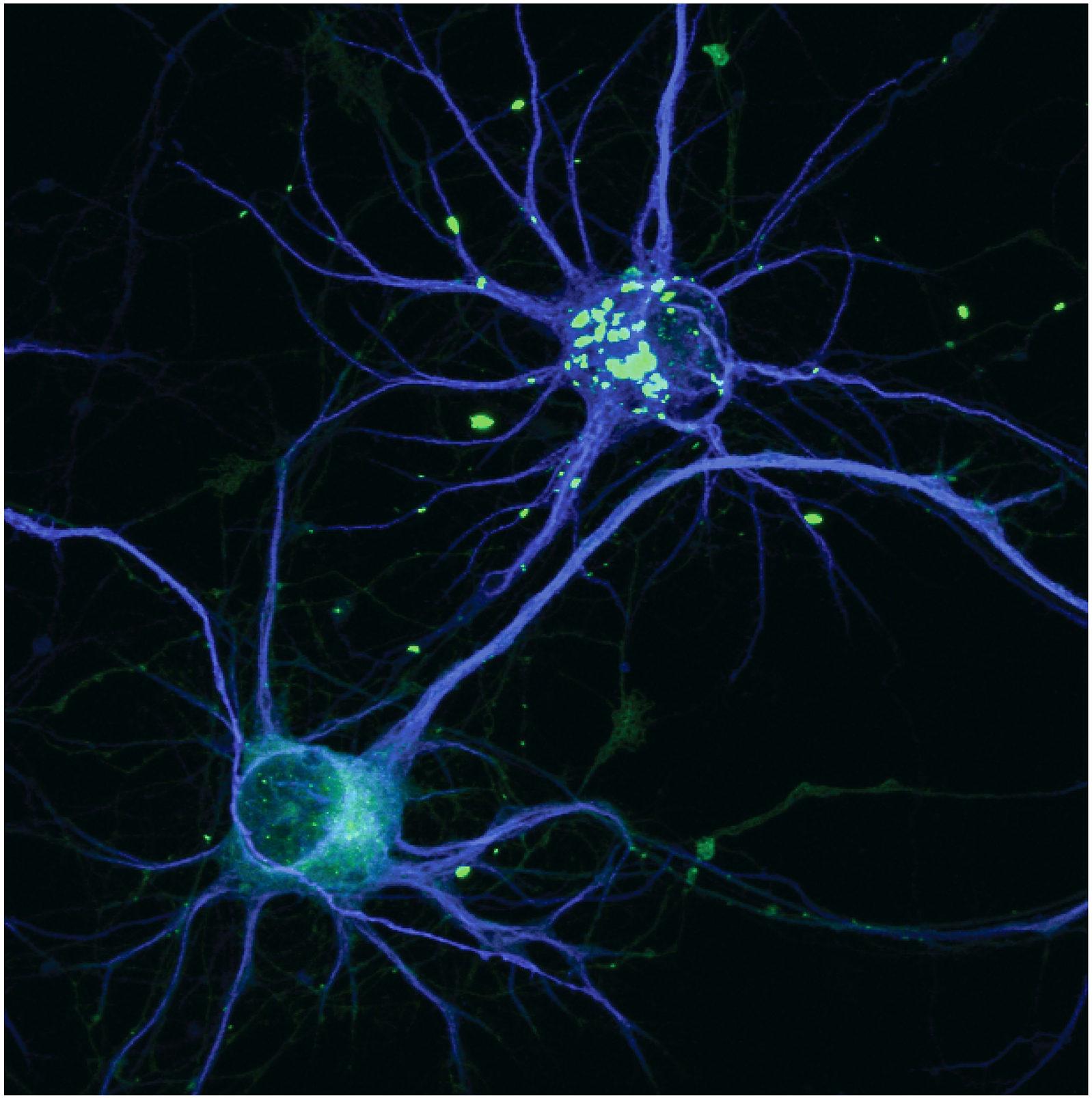
going to do everything we can, but your baby's going to die,'" says Russell Butterfield, a pediatric neurologist at the University of Utah. (Butterfield has received consulting payments from Biogen.) "Instead that conversation switches to, 'We have this new drug, it's absolutely amazing. We need to get it in as soon as possible.'"

Evie Lewis, now four years old, receives a dose of Spinraza by a lumbar puncture every few months, and she recently had her 15th injection. Although she still faces some issues, such as having to eat through a feeding tube, she is able to walk, run and climb—things that Blakely was never able to do, Elliot says.

A PACKED PIPELINE

Following the success of nusinersen, researchers began to tackle other diseases associated with clearly defined genetic mutations, such as Huntington's. That led to the drug tominersen, which was developed by Ionis and licensed for clinical testing to pharmaceutical company Roche in Basel, Switzerland. It is thought to work by targeting CAG repeats on the RNA strand produced by both the normal and faulty *HTT* genes and tagging them for destruction by an enzyme called RNase H1. The results of a phase I/II clinical trial, which were published in 2019, revealed that tominersen lowered concentrations of the mutant version of huntingtin in the cerebrospinal fluid, without causing any serious side effects.

The success of the early Huntington's trial caught the attention of neurodegeneration researchers because tangles of protein are a key feature of many such disorders. "There was a lot of excitement about this because it really opened up the doors to be able to do antisense trials for other neurodegenerative diseases where buildup of a toxic mutant protein plays a role," says Sarah Tabrizi, a neurologist at University College London, who led the phase I/II trial of tominersen.



A toxic version of the HTT protein, which causes Huntington's, forming clumps (*bright green*).

K. W. DROMBOSKY ET AL.

But an unexpected announcement at the end of March dealt a big blow to the Huntington's community. A phase III trial of tominersen involving 791 participants from 18 countries was terminated early on the advice of an independent committee of experts, who had conducted a planned review of the data. A statement from Roche said that no new safety concerns had emerged but that the drug's potential benefits did not outweigh the risks. Until more details are published, it's not possible to say what went wrong, Tabrizi says.

Drugs that work in a similar way to tominersen are still in play for other disorders with similar causes. Some cases of ALS, for instance, are caused by too much of a mutant protein, and a handful of ASOs for those forms of the disease are in clinical trials. The furthest along is tofersen, an ASO developed by Ionis to treat an inherited form of ALS. Tofersen is now being tested in a Biogen-sponsored phase III trial.

Claudia Testa, a neurologist at Virginia Commonwealth University, says that there are unique challenges that come with reducing the levels of a mutant protein, as tominersen and tofersen do, compared with boosting a missing one, as nusinersen does. Several protein-lowering strategies actually reduce levels of both good and bad versions of a protein. Scientists do not yet know the long-term effects on the diseases concerned, and it's not clear if this was the issue in the phase III trial of tominersen. The drug for SMA is doing something fundamentally different, "so it doesn't predict efficacy for the other diseases—and that's a painful truth," Testa says.

To avoid this problem, some ASOs are aimed squarely at mutant proteins. One biotechnology company, Wave Life Sciences in Cambridge, Mass., is testing a strategy that targets tiny mutations that sometimes occur alongside the CAG repeats on just the mutant copy of *HTT*. The aim is to leave levels of healthy huntingtin relatively intact. But the drug would work only in a subset of people with Huntington's who carry these mutations. Furthermore, that difference can be identified only with an exhaustive sequencing method that is not routinely carried out in the clinic, Testa says. (Testa has received consulting fees from Wave Life Sciences.)

More recently, researchers have started testing ASO-based therapies for more common neurodegenerative conditions, such as Parkinson's and Alzheimer's. The vast majority of cases are not linked to a specific genetic mutation, and these disorders are much more prevalent than are inherited diseases. The ASO for Alzheimer's aims to lower levels of tau, a protein that builds up into toxic tangles in the brain. For Parkinson's, the goal is to lower the α-synuclein protein, which aggregates into pathological clumps known as Lewy bodies.

But for neurogenerative diseases such as these, several genes in a network are likely to be involved, says Kevin Talbot, a neurologist at the University of Oxford, who will be involved in a forthcoming trial of an ASO for ALS. It's unclear how a change to one gene in the network would affect the rest, he says. (Talbot has previously served on scientific advisory boards for Roche and Biogen.)

Another issue, according to Talbot, is that these drugs currently need to be delivered using repeated lumbar punctures to reach their targets in the central nervous system. Before ASOs can be applied to a wider range of diseases, it will be important to find a way to get these drugs past the blood-brain barrier so as to deliver them less invasively, Talbot says. "There's a whole list of things that have to be done before we get too triumphalist."

CHANGE OF IDENTITY

Studies in mice suggest that the ASOs of the future could have even more powerful uses in the brain: replacing lost neurons.

Last year Xiang-Dong Fu, a cell biologist at U.C. San Diego, and his colleagues demonstrated that it is possible to use ASOs to convert nonneuronal brain cells called astrocytes into neurons. The team injected an ASO into a region of the mouse brain from which neurons are lost in Parkinson's. Once there the drug activated a network of genes that prompts astrocytes to become neurons. In mouse models of Parkinson's, Fu's team found that animals that received the treatment showed improvement in certain behaviors.

Cleveland, who was involved in Fu's trial, has been working with an ASO supplied by Ionis to test the idea in other parts of the brain. "This is really where I'm going to invest the rest of what I've got left as a career," he says. "I'm confident that we have only begun to think about the possibilities."

These astrocyte-converting ASOs are still at an early stage. Fu cautions that before this technique is taken to the clinic, it needs to be tested in nonhuman primates because their brains match our own more closely than do those of mice.

For now researchers are eagerly awaiting the results of the tofersen phase III trials in ALS and for more information about exactly why the tominersen trial for Huntington's was halted.

Susan, a retired nurse in her mid-60s, has been involved in the tominersen trial since phase I. She is disappointed in the news, she says, but is grateful for the care she has received as a participant. "I've been so privileged to be part of this trial right since day one. Now it's just about patience and reviewing. There's no alternative, is there?" SA

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Unraveling the Complex Link between COVID and Diabetes

Infection with the pandemic-causing virus seems to trigger diabetes in some patients. Here are five plausible explanations as to why

By Claudia Wallis

WILLIE B. THOMAS *GETTY IMAGES*

Claudia Wallis is an award-winning science journalist whose work has appeared in the *New York Times*, *Time*, *Fortune* and the *New Republic*. She was science editor at *Time* and managing editor of *Scientific American Mind*.

When COVID-19 began its inexorable march across the planet, doctors noticed that diabetes was among the conditions that make people particularly vulnerable to the new infection. Diabetic patients are three times as likely as nondiabetics to develop a severe case of COVID, and they are two to three times as likely to die of it.

Doctors noticed something else as well: patients with no history of diabetes sometimes developed severe diabetic symptoms while battling COVID, and some remained diabetic after COVID resolved. According to a meta-analysis of eight studies published in late November 2020, as many as 14 percent of hospitalized COVID patients developed what appeared to be "new-onset" diabetes.

Can the pandemic virus, SARS-CoV-2, directly trigger diabetes, or does something else explain these COVID-related cases? That question is the subject of a heated scientific debate and investigations that may ultimately lead to a better understanding of both ailments.

Muddying the waters are several confounding factors, such as the fact that any acute illness can disturb glucose metabolism, that COVID treatment can also impact blood sugar, and that conflicting data exist on whether or not SARS-CoV-2 can invade insulin-producing cells in the pancreas.

"The relationship between COVID-19 and diabetes is very complex," says Francesco Rubino, chair of metabolic and bariatric surgery at King's College London, "and it might involve more than one issue."

To help solve the puzzle, Rubino—along with two King's colleagues and Paul Zimmet, professor of diabetes at Australia's Monash University and a co-author of the meta-analysis—have established an international registry called CoviDIAB to compile extremely detailed case histories of new-onset diabetes in COVID patients. Their announcement of the registry in an August 2020 issue of the *New England Journal of Medicine* drew responses from hundreds of clinicians around the world, and so far about 165 completed case reports have been submitted. Preliminary analysis of the data will likely begin when at least 200 cases are registered, Rubino says.

In the meantime, he and Zimmet and other experts point to at least five explanations for the sudden appearance of diabetic symptoms in patients with COVID. All of them may be playing a role.

1. The virus may directly attack insulin-producing beta cells in the pancreas. Diabetes is fundamentally a disease of insufficient production of, or response to, insulin, the hormone that enables cells to use glucose as a fuel. In type 1 diabetes, which often strikes in childhood or adolescence, people lack the capacity to produce insulin because the beta cells in the pancreas have been destroyed by antibodies that target the body's own proteins. In type 2 diabetes, the more common form, body cells have become less sensitive to insulin, and beta cells are depleted or dysfunctional.

Perhaps the biggest point of contention about diabetes and COVID is whether or not SARS-CoV-2 directly attacks and destroys the specialized beta cells in the pancreas that produce insulin. There is evidence for and against this idea. For example, a study conducted in 2020 at Cornell University showed that insulin-producing cells cultured in a laboratory express ACE2 receptors—the key doorway through which SARS-CoV-2 enters human cells—and that the virus can invade these cells. A 2010 study also found ACE2 on beta cells and suggested that the earlier SARS-CoV virus could use the receptors to enter and destroy those cells. Zimmet says that there is further evidence from postmortem studies of COVID patients showing the destruction of pancreatic beta cells. "I won't say I am 100 percent convinced, but it's a very, very plausible explanation," he says.

Others are less persuaded. A study led by researchers at Vanderbilt University and published in *Cell Metabolism* in December 2020 searched for expression of the ACE2 protein in beta cells and found only negligible amounts. A second protein called TMPRSS2 that also plays a role in coronavirus entry to cells was largely absent as well. "We really thought this might explain how the virus got into beta cells, but we did not find the necessary proteins there," says Alvin C. Powers, director of the Vanderbilt Diabetes Center and a senior author of the study. "Negative findings are less exciting but very important. We are confident of our results." He notes that a second study published in the same issue of *Cell Metabolism* came to the same conclusion.

2. The virus may indirectly attack insulin production. While scientists may disagree about whether SARS-CoV-2 can directly enter beta cells, there is evidence suggesting that it can attack other parts of the pancreas. Both of the *Cell Metabolism* studies found that viral entry proteins were expressed elsewhere in the pancreas and in the small blood vessels that nourish beta cells.

"One could envision a scenario in which the virus could affect these micro blood vessels and beta cells could die," Powers suggests. Or it could infect other areas of the pancreas, inducing inflammation that disrupts insulin production, he adds.

The virus might also bring on diabetes by attacking or inflaming other organs and tissues that are involved in glucose metabolism. ACE2 receptors are plentiful in the intestines, blood vessels and liver, Rubino notes: "What happens if [viral infection] creates a dysfunctional intestine that doesn't do its normal job in regulating blood sugar levels? What happens if the virus interferes with liver function, which is also so crucial?"

Even more concerning, Rubino says, is a scenario in which the virus enters several organs at once, creating multiple disruptions. "That could end up creating forms of diabetes that we haven't seen before. Not type 1 or type 2 but something in between, something atypical."

3. Acute illness and inflammation are causing symptoms of diabetes. Doctors have known for decades that any severe health event—pneumonia, heart attack, stroke, trauma—can cause blood glucose levels to spike, a condition called hyperglycemia that is a signature of diabetes. Stress-related hormones such as cortisol and adrenaline are believed to cause this elevation, which may subside when the patient recovers or may leave the patient permanently diabetic.

There is no doubt that severe COVID can impose the kind of stress that raises blood glucose in patients who have no history of diabetes and sends it sky high in those who do.

> **"The relationship between COVID-19 and diabetes is very complex, and it might involve more than one issue."**
> ***—Francesco Rubino***

Endocrinologist Alyson Myers sees this phenomenon daily in her role as medical director of inpatient diabetes at North Shore University Hospital in Manhasset, N.Y. Patients admitted there with COVID, she says, rarely have blood sugar levels in the normal range, which is below 140 milligrams of glucose per deciliter of blood. "They are usually coming in in the 200s," whether they have a history of diabetes or not, and some arrive in an especially dangerous, hyperglycemic state called diabetic ketoacidosis, more typically seen in type 1 diabetes. "So it's not just new onset, but new onset of this severe form," Myers says.

Hyperglycemia on admission is a predictor of mortality, Myers says, "so you want to get that sugar down as quickly as possible." It's not unusual for hospitalized COVID patients to be given very large doses of insulin, even if they never required it in the past.

4. Treating COVID with steroids raises blood sugar. A standard treatment for severe COVID-19 at Myers's hospital and many others is a combination of the antiviral drug remdesevir and high doses of a steroid drug such as dexamethasone, which tamps down inflammation. The latter drug, however, raises insulin resistance and may therefore make hyperglycemia even worse.

This treatment, too, is a reason that COVID patients may suddenly develop severe symptoms of diabetes. "Between the COVID and the steroids, their blood sugar is through the roof," Myers says, "and we have to give them really high doses of insulin to combat that."

5. New-onset diabetes might not actually be all that new. The fact that a patient has no recorded history of diabetes does not mean that they weren't already diabetic or prediabetic or predisposed to the disease by virtue of genetics, obesity or some other factor.

All these conditions are remarkably common. In the U.S., for example, the Centers for Disease Control and Prevention estimates that 10.5 percent of people have diabetes, one fifth of whom have not yet been diagnosed. Another 34 percent of the adult population has elevated blood sugar in the prediabetic range.

"Diabetes is typically a silent disease for a very long time," Rubino says. "Estimates are that you may have it for five or more years without knowing it."

One way to tell whether silent diabetes was already present in COVID patients, Rubino notes, is with a commonly used blood test called A1C that indicates average blood sugar levels for the previous three months: "A normal A1C allows you to be more confident that there wasn't any diabetes two or three months ago." Where available, A1C data will be an illuminating component of the CoviDIAB registry, as will follow-up data showing whether COVID-related diabetes vanishes as suddenly as it arose or if it persists.

Understanding precisely how the coronavirus disrupts glucose metabolism could help resolve long-standing questions about the role other infections play in diabetes. Viruses such as Coxsackie B and rubella are known to be associated with some cases of type 1 diabetes, but small data sets have made it difficult to pin down a mechanism. "With a pandemic we will probably see more cases than we've ever seen before," Rubino says. "That's why the story of COVID and diabetes is important for the understanding the role of viruses in causing diabetes." SA

Tomorrow's Biggest Microbial Threats

Health experts around the world are focused on SARS-CoV-2, but similar viruses and microbial organisms such as bacteria could create the next global killer

By Mike May

MARINA SPENCE *NATURE MEDICINE*

Mike May is a freelance writer based in Bradenton, Fla.

IN THE MIDST OF THE RAMPAGE OF COVID-19—WITH MORE than 154 million confirmed cases and more than three million deaths globally—it is difficult to even consider the possibility of something similar lying in wait for the next opening in human vulnerability to disease. But that is exactly what health experts around the world must contemplate to prevent or reduce the impact of other potential causes of a pandemic. Equally important, that thinking should already be underway, and it is.

FEAR OF THE KNOWN

The unknown—in this case, novel and maybe even unimaginable diseases—creates the most fear for some people, but there are plenty of known types of diseases to worry about, and some experts see those as the most dangerous. For instance, Amesh Adalja, an expert in preparing for pandemics and a senior scholar at the Johns Hopkins Center for Health Security, says, "The biggest threats are still going to come from ones that we've already characterized." For a top global threat, Adalja picks influenza virus, noting that it "has proven time and time again that it's capable of causing pandemics, and based on its genetic structure it's really only a matter of time before new strains emerge that have the capacity for efficient human-to-human transmission."

There is a list of deadly influenza outbreaks. The 1918–1919 influenza pandemic killed an estimated 50 million people, which was about 2.5 percent of the world's population. About one million people died in the 1957–1958 influenza pandemic, and there have been others. Influenza is not the only known threat, however.

As SARS-CoV-2 continues to ravage many areas around the globe, other members of the coronavirus family should not be ignored. The U.S. Centers for Disease Control and Prevention lists seven coronaviruses that can infect humans, but overall there are hundreds of coronaviruses. Although the respiratory syndromes MERS and SARS, both caused by coronaviruses, did not spread very efficiently among humans, Adalja says that "the events this year have shown that this viral family must be taken much more seriously than it had been in the past." For example, MERS is not easily transmitted between people, but about 35 percent of the people who get it die—which makes it far more deadly than COVID-19.

In 2018 Adalja wrote: "The most probable naturally occurring [global catastrophic biological risk]-level threat that humans face is from a respiratory-borne RNA virus, and so this class of microbes should be a preparedness priority." He was right because SARS-CoV-2 is just such a virus. Thinking even more broadly, he now says that "any kind of efficiently spreading respiratory virus, whether or not it comes from influenza or coronavirus families, should also be thought of as potentially having pandemic potential because they all have these similar characteristics in that they spread efficiently from human to human."

REACTING TO RESISTANCE

In addition to defending against coronaviruses, public health experts must also defend against other known microbial threats, such as antimicrobial-resistant (AMR) bacteria. Even now these microbes cause about 700,000 deaths a year around the world, and multidrug-resistant tuberculosis accounts for about one third of those. Experts already forecast far more AMR-related deaths ahead, with the United Nations Interagency Coordination Group on Antimicrobial Resistance warning that drug-resistant disease could kill 10 million people a year by 2050.

According to Linfa Wang, a professor in the Program in Emerging Infectious Diseases at Duke–National University of Singapore Medical School, AMR bacteria remain a key concern, but he says, "at least we can do systematic and targeted surveillance and monitoring, which will provide some early warning."

Despite such recognition of the potential danger from AMR bacteria, few drugmakers have addressed the growing concerns. "Common bacterial infections will continue to build resistance to antibiotics, and we have very little new developments in antibiotic portfolios of pharmaceutical companies," says Moses Alobo, program manager for Grand Challenges Africa at the Alliance for Accelerating Excellence in Science in Africa, which is headquartered in Nairobi, Kenya, and COVID-19 chair of the African Academy of Sciences. "There is, therefore,

a threat from antimicrobial-resistant species from our hospitals."

INTERSPECIES INTERACTIONS

Infectious agents that jump from nonhuman species to humans—even ones beyond coronaviruses—also appear to be increasingly dangerous. "There are millions of animal viruses for which a jump to humans becomes increasingly likely as our populations and those of our livestock grow and expand into new territories and niches," says Iruka Okeke, a professor of pharmaceutical microbiology at the University of Ibadan in Nigeria. "But between now and when that happens, millions of people will be sickened and/or killed by existing pathogen threats."

Many existing zoonotic threats create intense public health challenges. As examples, Alobo points out that "viral hemorrhagic fevers like Ebola, Marburg, Lassa fever, and yellow fever will be potentially hazardous." Some of these infections are far more deadly than infection with SARS-CoV-2. On average, Ebola virus kills about half of the people it infects, but some outbreaks killed 90 percent of the people infected. Fatalities from Marburg virus are about the same.

Keeping track of zoonotic diseases also poses a problem. For emerging zoonotic diseases, Wang says, "We don't have a reliable and affordable monitoring system yet, so the responses will always be reactive rather than proactive."

Plus, there is so much to monitor. Over than a decade ago, scientists reported that more than 70 percent of new pathogens come from animals. It will be difficult to stay ahead of these potential threats.

WORKING WITH THE UNKNOWN

In many ways, health-care systems will remain reactive to deadly infections. For example, Kevin Marsh, senior adviser for the African Academy of Sciences, says, "It is in the nature of such threats that we can't predict the next one in either timing or pathogen, but we can be pretty sure that there will be new ones." So, he says, "the key is active surveillance and having mechanisms for rapid identification and response to new outbreaks."

A sophisticated surveillance system might even prevent another disease from spreading around the world so fast. "The world needs to build proper microbial surveillance networks to monitor any developments in infections within regions—essentially have a pathogen genetic surveillance group that concentrates on these activities," Alobo states. "Early-warning systems are needed."

Warning systems would help. In the face of so much uncertainty, however, health-care systems cannot afford to wait on outbreaks before reacting.

SCIENCE MEETS SOCIETY

Perhaps as much as anything else, some public reactions to COVID-19 surprised experts. A year ago Okeke believed that the biggest challenge with an emerging microbial threat would come from detecting it and developing a vaccine. Now, after watching the reaction to COVID-19, she says the biggest challenge "will be convincing people to take the steps that are necessary to protect humankind from a threat." Despite the rapid success in detecting SARS-CoV-2 and developing several effective vaccines, Okeke says, "it has been impossible to make people stay home or masked to avoid transmission in most countries." She adds, "When given the choice between skipping a holiday and posing mortal risk to another's life, sufficient numbers of people have chosen the latter, and we have to presume they will do it again." Thus, preparation goes beyond science and deep into societies around the world.

Figuring out how to accomplish that will depend on many forms of research. For instance, Okeke says, "I would like to see some political, social and behavioral science research so that public health can be better informed about how to convince or persuade people to make life-saving decisions in epidemics."

The need for improved policy decisions does not stop with citizens or hospitals. As Wang discusses, "The real difference will come from policy and legal framework changes in the context of transparent and efficient reporting of 'unusual cases' and a united international system of pandemic preparedness that is as far away from geopolitics as possible."

At the same time, more basic science should be pursued. Here Okeke recommends more research into infectious disease biology, including epidemiology, microbiology, immunology and vaccine development. Such studies could help scientists predict the next big threat, as well as its most likely source, and even to "stall it in its tracks faster and respond to it even faster than the record times seen with COVID-19," Okeke explains.

TAKING AN ONGOING PERSPECTIVE

Instead of focusing on the biggest disasters in global health, such as the 1918 influenza and current COVID-19 pandemics, public health experts know that people always face serious problems with infectious disease. With investment in ongoing research around the world, many benefits could arise. "In addition to averting the next public health disaster, this would also make it possible to address endemic threats that have plagued us for centuries and will continue to do so without a concerted push for discovery and action," Okeke says.

The world might never be free of microbial threats, but research combined with technology could greatly reduce the odds of diseases getting out of control. Achieving that goal, however, depends on staying ahead of these diseases whenever possible. SA

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Stacey Colino is an award-winning writer specializing in health and environmental issues and a regular contributor to *U.S. News & World Report.*

THE BODY

Reproductive Problems in Both Men and Women Are Rising at an Alarming Rate

A likely culprit is hormone-disrupting chemicals

GETTY IMAGES

When you see or hear a reference to "the 1 percent," most people think of socio-economic status—the people with the top 1 percent of wealth or income in the U.S., which is how the term is commonly used in our culture.

Not us, though.

What we think of is the fact that reproductive problems in males on the entire spectrum are increasing by about 1 percent a year in Western countries. This "1 percent effect" includes the rates of declining sperm counts, decreasing testosterone levels and increasing rates of testicular cancer, as well as a rise in the prevalence of erectile dysfunction. On the female side of the equation, miscarriage rates are also

increasing by about 1 percent a year in the U.S., as is the rate of gestational surrogacy. Meanwhile the total fertility rate worldwide has dropped by nearly 1 percent a year from 1960 to 2018.

When people hear of this, there's often a natural instinct to shrug it off, believing that 1 percent a year isn't really a big deal. But it is a huge deal! It adds up to more than 10 percent a decade and more than 50 percent over 50 years. When you consider that sperm counts declined by 50 percent in just 40 years, as Shanna's meta-analysis published in a 2017 issue of the journal *Human Reproduction Update* showed, it's difficult to deny or discount how alarming this is.

So we continue to wonder: Where is the outrage on this issue? The annual 1 percent decline in reproductive health is faster than the rate of global warming (thankfully!)—and yet people are up in arms about global warming (and rightly so) but not about these reproductive health effects. To put the 1 percent effect in perspective, consider this: scientific data show a 1.1 percent a year increase in the number of children diagnosed with autism spectrum disorder between 2000 and 2016, according to the Centers for Disease Control and Prevention. People have been rightly unnerved about this.

Why aren't people equally troubled by reproductive damage to males and females? Maybe it's because many don't realize that these worrisome changes are happening or that they're marching along at the same rate. But everyone should. After all, these reproductive changes can hardly be a coincidence. They're just too synchronous for that to be possible.

The truth is, these reproductive health effects are interconnected, and they are largely driven by a common cause: the presence of hormone-altering chemicals (a.k.a., endocrine-disrupting chemicals, or EDCs) in our world. These hormone-hijacking chemicals, which include phthalates, bisphenol A, and flame retardants, among others, have become ubiquitous in modern life. They're in water bottles and food packaging, electronic devices, personal-care products, cleaning supplies and many other items we use regularly. And they began being produced in increasing numbers after 1950, when sperm counts and fertility began their decline.

Exposure to these chemicals is especially problematic during pregnancy because what happens during pregnancy doesn't stay in pregnancy. Rather an expectant mother's exposure to toxic chemicals in the air she breathes, the water she drinks, the foods she eats and the products she slathers on her skin can enter her body (and hence the fetus) and influence her baby's reproductive development. This is particularly true early in pregnancy—in what's called the reproductive programming window—and it's especially true for male babies.

For example, if a woman is exposed to chemicals that block the action of androgens during the first trimester of pregnancy, this can affect the reproductive development of the male fetus in numerous ways. It can result in a shortening of the anogenital distance (AGD), the span from the anus to the base of the penis, which is significant because research has shown that a shorter AGD correlates with a smaller penis and, in the adult, a lower sperm count. In addition, prenatal disruption of the male hormonal system can result in reduced testosterone levels and increase the risk that a baby boy will have undescended testicles (cryptorchidism) or a particular type of malformed penis (hypospadias) at birth. And if a boy is born with these genital defects, he will have an increased risk of low sperm count and testicular cancer as an adult.

This cluster of related reproductive problems—for both men and women—is presenting huge challenges to the world's population. There's the obvious challenge related to fertility issues and the declining birth rate. But endocrine disruption is also a culprit in rising rates of autoimmune disorders as well as the growing epidemic of obesity and metabolic syndrome (a cluster of conditions that increases the risk of heart disease, stroke and type 2 diabetes). Some of these reproductive effects are even associated with an increased risk of premature death.

To put it mildly, these issues are more important than the "1 percent" people usually pay attention to, which means: We need to shift our collective focus. It's time for us to make it a priority to demand that endocrine-disrupting chemicals in the everyday products are replaced with chemicals that don't affect our hormones and don't persist in the environment. It's also time to establish better testing methods and regulatory actions so that only safe chemicals can enter the market and our bodies. In other words, we need to stop using one another and our unborn children as lab rats for EDC exposures. The health and the future of the human race really do depend on it.

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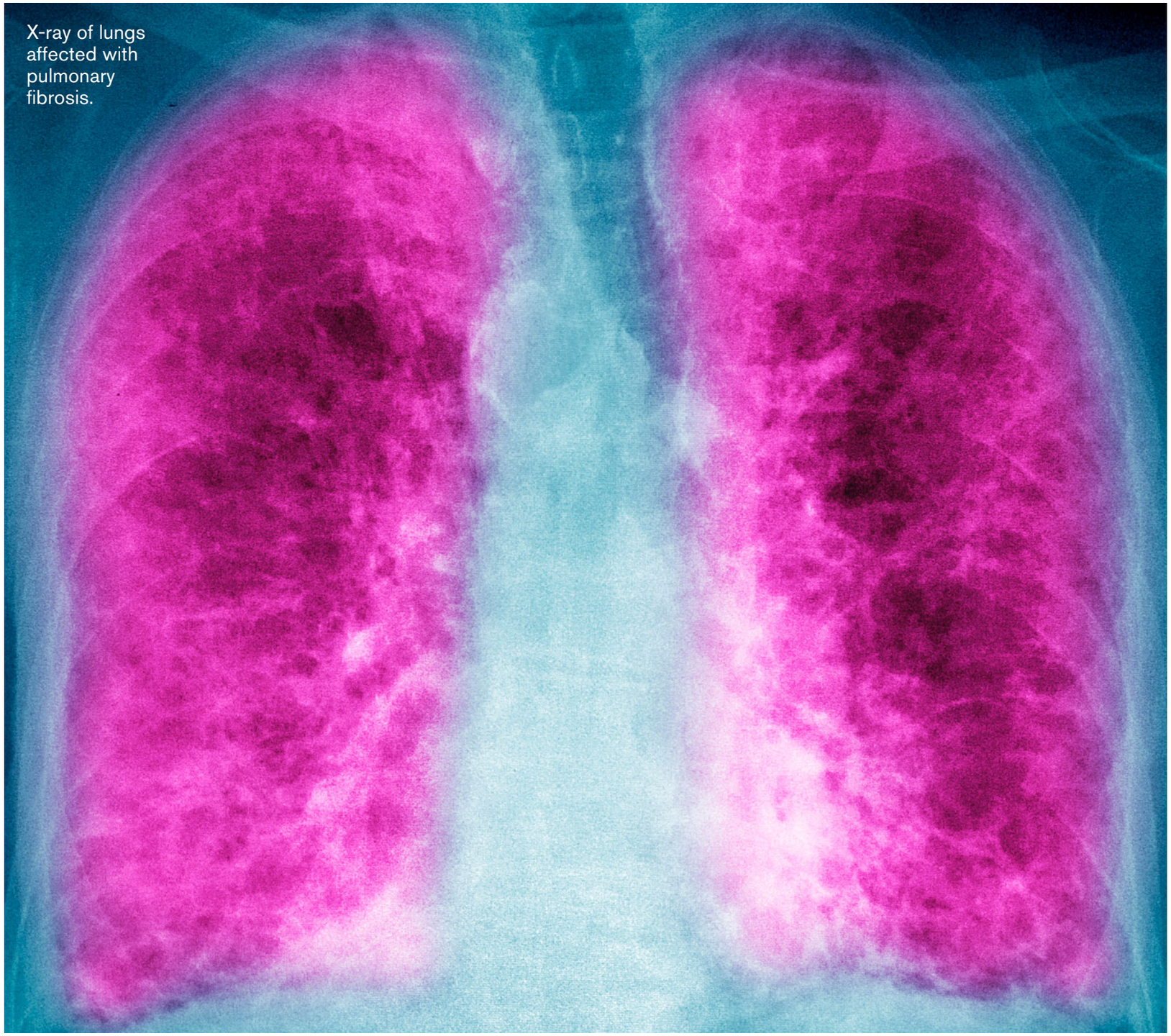
MEDICINE

The Deadly Lung Disease You've Probably Never Heard Of

Pulmonary fibrosis is diagnosed in about 50,000 new patients annually, and as many as 40,000 Americans die from it every year



X-ray of lungs affected with pulmonary fibrosis.

GETTY IMAGES

Pulmonary fibrosis (PF) is an uncommon and frequently fatal lung disease, and the road to diagnosis can be long and difficult. No one is certain how many people are affected by it. Research estimates that idiopathic pulmonary fibrosis (IPF), which is just one of more than 200 types, affects one out of 200 adults older than 70 in the U.S. That translates to more than 200,000 people living with IPF today. Approximately 50,000 new cases are diagnosed annually, and as many as 40,000 Americans die from IPF every year.

There are many factors that make this disease difficult for both patients and providers. Not only is there a protracted time to diagnosis (and sometimes misdiagnosis), but patients

also experience debilitating symptoms. Unlike diabetes, heart disease or cancer, where awareness is high and medical terminology is easy to access, PF is a condition that most people haven't heard of until they are given the diagnosis. In fact, nearly nine in 10 Americans do not know the symptoms of PF, according to a recent survey by the Pulmonary Fibrosis Foundation (PFF). Seeking out expertise where it exists is critically important to the earlier diagnosis and management of this patient population.

The 200-plus different lung conditions that qualify as PF all look very much alike. In its simplest sense, pulmonary fibrosis literally means scarring in the lungs: the word "pulmonary" means lung, and the word "fibrosis" means scar tissue. When you have a process that leads to scarring or inflammation of the lung, over time the scar tissue can destroy the normal lung, making it difficult for oxygen to pass easily into the bloodstream. The lungs become stiff, making it challenging for patients to take a deep breath.

Some known causes of PF are aging (those older than 60), cigarette smoking (both current and past smokers) and genetics. We also know that as part of the systemic disease process, patients can develop PF alongside an autoimmune condition, such as rheumatoid arthritis or scleroderma. There are also environmental causes, such as exposure to mold or animal proteins (especially from indoor or caged birds), which lead to a disease called hypersensitivity pneumonitis (HP). Other causes include certain medications, such as chemotherapy and amiodarone, which can sometimes lead to drug toxicity and PF. On the other hand, there are many suffering from these diseases whose cases cannot be attributed to a specific cause—the definition of "idiopathic." All these diseases share one unifying feature, however: inflammation and scarring of the lungs.

Unlike diabetes, heart disease or cancer, where awareness is high and medical terminology is easy to access, PF is a condition that most people haven't heard of until they are given the diagnosis.

PINPOINTING PF

The symptoms of PF make this disease difficult to diagnose as they are nonspecific. Symptoms can range from being asymptomatic to having a chronic dry cough, shortness of breath and/or fatigue. Because symptoms are similar to other illnesses, like the common cold, or may appear mild or absent early on, many patients are not diagnosed until the disease progresses to its later stages. That is why a precise and early diagnosis is crucial.

There are a few tests we use to determine if a patient has PF. Doctors will look for low oxygen levels, "crackles" in the lungs (which sound like Velcro being pulled apart) or clubbing of the fingers. In addition, high-resolution computed tomography (HRCT) tests have changed the way we diagnose patients with PF. HRCT scans give a close-up view of the lungs, providing more detail than routine CT scans. Many forms of PF look similar on a CT scan to the untrained eye, but subtle findings on HRCT scans are critically important when trying to identify which type of PF a patient might have. Through a lot of research, we are able to diagnose the type of PF by combining the clinical history and appearance on an HRCT scan in up to 50 percent of cases. A doctor may also perform a lung biopsy, which can help determine the type of PF and which treatments might be effective.

WHY PF IS A PROBLEM

After diagnosis, PF significantly affects the quality of life for patients, who may become breathless while taking part in everyday activities, such as showering, getting dressed, speaking on the phone or even eating. Patients need to think ahead, analyzing every single activity they plan to take, and rethink social participation, because a chronic cough might prevent them from taking part in conversations. Many also become dependent on a caregiver, along with a wider support network. All these things can be very challenging for someone living with PF.

In short, PF is a serious, life-limiting illness. While the average survival rate for certain forms of PF is only three to five years, the earlier diagnosis and better treatments now available allow many people to live much longer. Fortunately, we have a number of ways to treat PF, includ-

ing oxygen therapy, pulmonary rehabilitation, the use of medications and even lung transplantation. In 2014 the FDA approved two medications for IPF: nintedanib and pirfenidone. That was a huge success for our community, but it's only the beginning of what we need to be doing for our patients.

LOOKING AHEAD

This year holds much promise with advancements in research and clinical trials. The research community is aggressively investigating new therapeutics for all forms of PF. For example, PRECISIONS, an NIH-supported study, is looking at genetic risk factors and responses to therapy, applying the principles of precision medicine to the treatment of IPF patients.

Now more than ever, there are many opportunities for patients to participate in clinical trials, and the PFF plays a key role in supporting those trials. We also have the PFF Registry that allows patients to participate in a very positive way to help accelerate research efforts. With patient participation and collaboration with various funding agencies and investigators, we will continue to make advancements for patients with PF.

My hope is that by spreading useful information and providing helpful resources, the visibility of PF will continue to grow, leading to improved early detection and quality of life. We're looking forward to patients living longer and better lives with this condition.

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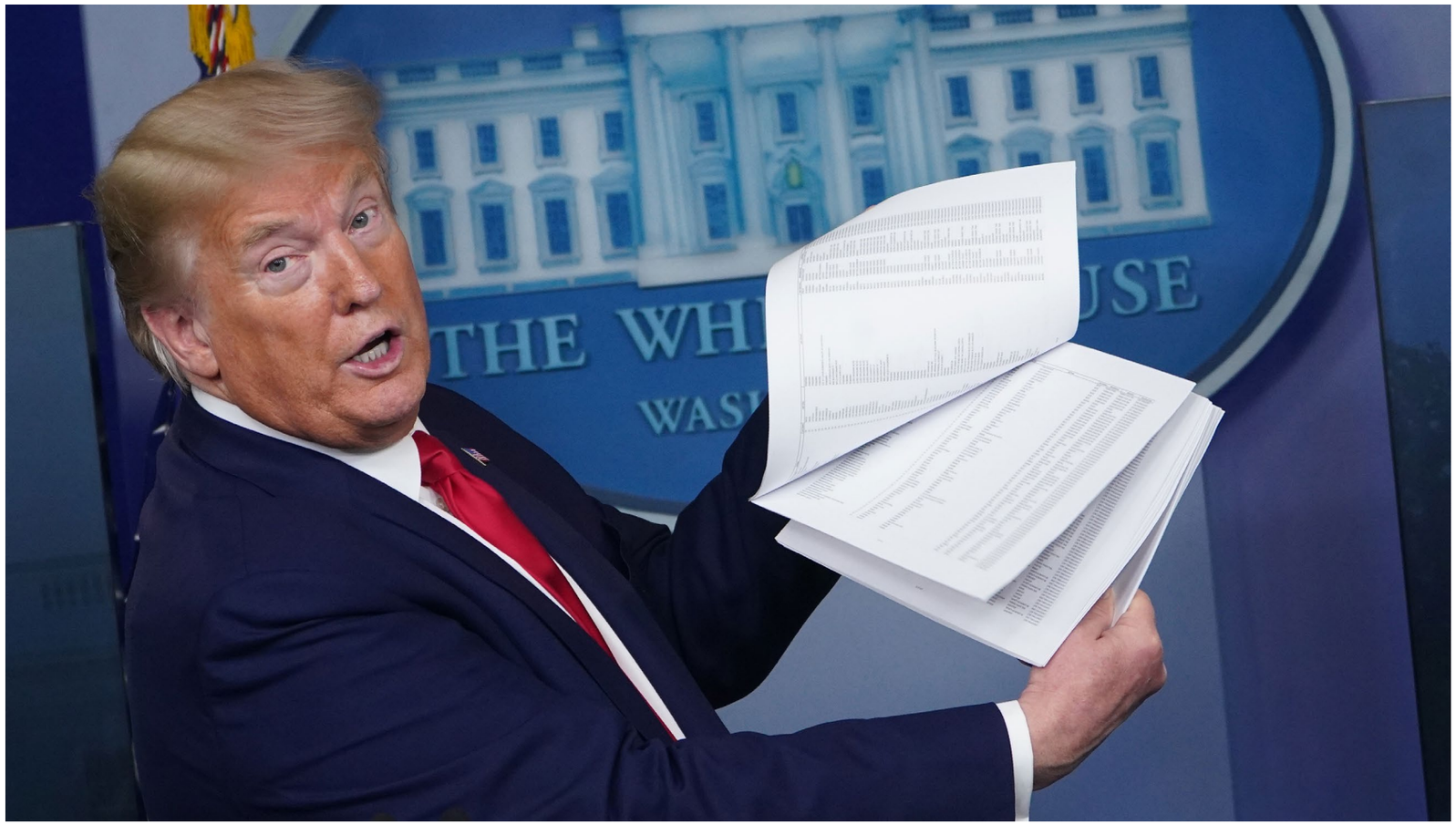
POLICY & ETHICS

Trump's Policy Failures Have Exacted a Heavy Toll on Public Health

But things were on the decline long before he took office



Then U.S. president Donald Trump holds up papers displaying federal locations for testing during the daily briefing on the novel coronavirus, COVID-19, in the Brady Briefing Room of the White House in Washington, D.C., on April 20, 2020.

MANDEL NGAN *GETTY IMAGES*

In the final year of Donald Trump's presidency, more than 450,000 Americans died from COVID-19, and life expectancy fell by 1.13 years, the biggest decrease since World War II. Many of the deaths were avoidable; COVID mortality in the U.S. was 40 percent higher than the average of the other wealthy nations in the Group of Seven (G7).

In a *Lancet* report by the Commission on Public Policy and Health in the Trump Era, released on February 20, we chronicled Trump's effects on population health. His incompetent and malevolent response to the COVID-19 pandemic capped a presidency suffused with health-harming policies and actions.

We also found, however, that Americans' health began lagging before Trump took office. In 1980 U.S. life expectancy was similar to that of other G7 nations; by 2018 it was 3.4 years shorter. In 2018 461,000 deaths would have been averted if U.S. life expectancy had kept pace with the rest of the G7. That's equivalent to the number of Americans who died from COVID-19 last year.

Faced with the pandemic, Trump suppressed scientific data, delayed testing, mocked and blocked mask wearing, and convened mass gatherings where social distancing was impossible. Despite the mounting threats of COVID-19 and global warming, he pulled the U.S. out of the World Health Organization and the Paris climate accord. He installed industry insiders in regulatory posts tasked with protecting Americans from environmental and occupational hazards; their regulatory

rollbacks resulted in 22,000 excess deaths from such hazards in 2019 alone. He pushed through a $1.9-trillion tax cut for the wealthy, creating a budget hole that he then used to justify cutting food and housing assistance for the needy. He tried, but failed, to repeal the Affordable Care Act, then bent every effort to undermine it, pushing up the number of uninsured Americans by 2.3 million. He denied entry to refugees fleeing violence, abused immigrant detainees, and penalized immigrants for accessing basic social services.

Although Trump bears special blame for America's health woes, many of his policies did not represent a radical break with the past. Both Republican and Democratic administrations have pursued economic, health and social policies deleterious to population health.

Richard Nixon's racially targeted war on drugs initiated mass incarceration, compromising the health of prisoners, their families and others in their communities. Starting in the Ronald Reagan era, financial deregulation, trade deals favoring corporations and attacks on union labor caused deindustrialization and increased income precarity in many parts of the country, contributing to an epidemic of "deaths of despair." Bill Clinton's welfare cuts and tough-on-crime measures compromised the life chances of many Americans, particularly Black and brown Americans. Market-based health-care reforms dating to Reagan, and endorsed by Democrats and Republicans alike, have commercialized and bureaucratized medical care, raising costs and shifting care toward the wealthy. And corporate lobbyists have blocked regulation of dangerous products such as firearms, obesogenic foods and addictive medications.

These long-standing policies have contributed to persistent race-based health gaps bequeathed by the legacies of slavery, Jim Crow segregation and Native American genocide, and widening gaps by income, education and geography. And the pattern of government neglect set the stage for the racist and nativist appeals Trump used to fuel his political rise. In 2016 Trump gained his largest electoral margins in counties with the worst mortality trends.

Fortunately, many of the policies needed to ameliorate COVID-19's damage would also begin to address the longer-standing mortality crisis. We need more than vaccinations. We need universal paid sick leave, Medicare for All, environmental and workplace protections, income supports and affordable housing to limit crowding and ensure food security, alternatives to incarceration, public health infrastructure, investments in education, and compensation to Native and Black Americans for the wealth and labor confiscated from them.

It is tempting, after the chaos of the Trump years, to seek a return to normal. But normal in the U.S. was deadly for hundreds of thousands of Americans every year. Our nation's public health and social policy infrastructure has suffered 40 years of neglect. Failing to repair it will ensure that the U.S. remains vulnerable to the next health crisis, that health inequities will persist and that our politics will remain mired in division.

As the Biden administration looks to the future, we need massive reinvestment in the conditions needed for a healthy population.

Virginia Sole-Smith is author of *The Eating Instinct: Food Culture, Body Image and Guilt in America.* Her next book, *Fat Kid Phobia,* will explore weight stigma and children's health.

BEHAVIIOR & SOCIETY

In Obesity Research, Fatphobia Is Always the X Factor

Contrary to what you've undoubtedly been told, you can be fat and fit at the same time

GETTY IMAGES

"Tell me what I'm missing," my husband said. He, like many of us, had seen headlines about a recent study that surveys the weight, exercise habits and cardiovascular disease risk of more than half a million people in Spain. It's being covered by media outlets as irrefutable proof that no, sorry, forget what the body positivity movement has told you—you cannot be both fat and fit. This is not a new argument. It's the comment made on every story I write, as a journalist who covers weight stigma (negative beliefs about large bodies that lead to discrimination against fat people). But in a burst of good news for Internet trolls, the authors of this new study, who published their findings as a research letter in the *European Journal of Preventive Cardiology*, drew this same conclusion because the people in their study with a high body mass index (BMI) had a higher risk of diabetes, hypertension and high cholesterol than the people with body mass index scores in the normal rage.

This relationship stood even when people in bigger bodies exercised regularly. Thus, "weight loss per se should remain a primary target for health policies aimed at reducing [cardiovascular disease] risk in people with overweight/obesity," the researchers wrote. So what's missing from that conclusion and this argument more broadly? Any acknowledgment of the way weight stigma (also known as fatphobia) impacted the study's design, the health of the participants, and our entire

understanding of weight and health.

Let's start by noting that these conclusions contradict several other recent pieces of research. A 2017 study published in the same journal followed 5,344 Dutch people older than 55 for 15 years and found that folks with high BMIs who also had high levels of physical activity showed no increased risk for heart disease compared with equally active people with normal BMIs. An analysis of data on 22,476 Americans aged 30 to 64 published in 2020 found that being physically active was associated with a larger reduction in a person's 10-year heart disease risk than having a normal BMI. Both these studies affirm the conclusion drawn in a 2014 meta-analysis of 10 studies that when it comes to mortality risk, fitness matters more than fatness.

But when researchers talk about these findings, they call them "the obesity paradox" because it's so startling to see fat people not dying of heart disease like we're always told they will. "The term 'obesity paradox' is a prime example of weight stigma in the scientific literature," Jeffrey Hunger, an assistant professor of social psychology at Miami University of Ohio told me when I wrote about medical weight stigma for the July 2020 issue of *Scientific American*. "Think about it: A paradox is something contradictory or seemingly absurd. This term came about because it was considered absurd that fat people could actually be healthy."

"Think about it: A paradox is something contradictory or seemingly absurd. This term came about because it was considered absurd that fat people could actually be healthy."
—Jeffrey Hunger

Weight stigma also shows up in the questions that scientists don't ask. In the new study, researchers took the participants' weight and health histories from medical records and asked them to self-report their activity levels. They did not track other established risk factors for heart disease, such as diet and smoking history. And they did not ask any of the participants whether the doctors examining them displayed signs of weight bias, even though we know from other research that many doctors discriminate against patients in large bodies.

In one survey, 24 percent of physicians admitted they were uncomfortable having friends in larger bodies, and 18 percent said they felt disgusted when treating a patient with a high BMI. You are unlikely to improve the health of someone you find repulsive, and indeed we see that doctors tend to undertreat, overtreat or even misdiagnose patients in bigger bodies, confusing tumors for fatness. And fat people are more likely to avoid medical care when they know they'll be treated badly, which means they are often sicker and harder to treat by the time they do see a doctor.

The researchers also did not ask their high-weight participants how the experience of fatphobia impacts their ability to be physically active in the first place. Can they find workout clothes that fit? Can they go to their local gym or for a walk in the park without fear of harassment? In her memoir *Happy Fat*, comedian Sofie Hagen recalls standing in a changing booth at her gym for 45 minutes, working up the courage to walk to the pool in her swimsuit and endure the stares of other slimmer swimmers. "Gyms are for thin people; staying home and eating chips is for fat people," she writes. "So for a fat person, going to a gym, or running in the park, or doing exercise in a place with people can be anxiety-inducing because you are so on display doing something that is considered uncharacteristic."

Last, the researchers did not consider whether the increased risk for heart disease found in their fat yet active subjects might be from the experience of living in that fat body rather than the fat itself. A 2016 analysis of data collected from more than 21,000 Americans found a significant association between a person's experience of weight stigma and an increased incidence of heart disease, stomach ulcers, diabetes and high cholesterol even after researchers controlled for their subjects' socioeconomic status, physical activity level and BMI. Other studies have shown that experiencing weight stigma consistently raises our cortisol levels and other physiological stress responses, which are tied to negative health outcomes.

But here's something the Spanish researchers find, despite their conclusion that you can't be fat

and fit: Being physically active reduced a person's risk of heart disease compared with the less active people in their same weight class. So a fat person who exercises may still be more likely to get diabetes or high blood pressure than a thin person, but the gulf is less enormous. (In fact, the study found that active people in the overweight BMI range had roughly the same risk for hypertension as inactive people in the normal BMI range.) More important, active fat people are less likely to get those conditions than if they didn't exercise at all. This means that you can still improve your health through physical activity even if you don't get skinny in the process. Which you probably won't; that's why so many of us have likely abandoned New Year's weight-loss resolutions. "To give the impression that changing your weight status from obese to overweight or normal weight is this straightforward, easy thing to do is to effectively ignore 50 years of research," says Marlene B. Schwartz, director of the Rudd Center for Food Policy and Obesity at the University of Connecticut.

That research usually gets ignored because weight loss sells. The diet industry was valued at $192.2 billion in 2019, according to a report by Allied Market Research. Weight-loss pharmaceuticals alone accounted for nearly $1.7 billion last year, according to another recent report. These industries, along with food manufacturers, have long funded much of the science that gets done on weight and health. And independent reviews, including a 2018 meta-analysis, have found that industry sponsorship influences research agendas.

The National Institutes of Health's decision in June 1998 to expand the obese and overweight categories on the body mass index to include 29 million more Americans preceded the FDA approval of two popular weight-loss drugs, Orlistat and phentermine. This past February, researchers at Northwestern University reported findings that semaglutide, a medication taken as a weekly injection, resulted in significant weight loss. The drug is currently marketed at a lower dose as a diabetes treatment and retails for around $1,000 a month; its potential for profit as a diet drug is enormous, especially because patients will have to take it for the rest of their life to avoid regaining weight.

When we define health and fitness exclusively through the prism of someone's pants size, we ignore the myriad of other measurements that matter more. Exercising regularly can build strength and flexibility, while reducing symptoms of anxiety and depression, and it improves biomarkers of health such as blood pressure and cholesterol—and that's just the start of the list. If people feel like they've failed at exercise because they didn't also get smaller, they'll miss out on all its other benefits. And when obesity researchers and doctors keep pushing people toward weight loss as our "primary target" for health, what they're really saying is that those other health benefits don't matter; that our bodies will never be good enough; that we'll never be good enough—unless we get thin. When researchers—or doctors or your mother or Internet trolls—say "you can't be fat and fit," what they really mean is, "you can't be fat and thin." This is true. But it also shouldn't be the goal.

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