August–September 2021

SCIENTIFIC AMERICAN
Health & Medicine

How Long Can We Live?

New research pins the maximum length of human life

EVERYTHING WE KNOW ABOUT COVID VACCINES SO FAR

WHAT HAPPENED TO THE FLU?

MRNA VACCINES FOR CANCER, HIV AND BEYOND

WITH COVERAGE FROM nature

Liz Tormes

Aging's True Tactics

For many cultures, including the U.S. and China, aging is a particular anathema. The global market for antiaging products alone is valued at more than $50 billion a year and is expected to balloon to more than $83 billion in less than a decade. The demand to slow aging–through mostly ineffectual pills, serums or creams--is real. But our understanding of how the human body ages is still nascent, one could argue. In fascinating new findings, a team of researchers determined that an ultimate limit to human life exists, mostly because the body's ability to bounce back from disease or other disruptions and reestablish a so-called equilibrium declines over time. So aging may be less about how quickly the body degrades and more about the body's overall resilience (see "Humans Could Live up to 150 Years, New Research Suggests").

For now one of the biggest threats to human life remains the COVID-19 pandemic. With nearly two billion doses administered, Nature reporter Heidi Ledford profiles everything we have learned so far about these new medicines (see "Six Months of COVID Vaccines: What 1.7 Billion Doses Have Taught Scientists"). And mRNA technology may open the door for new treatments against an array of diseases beyond COVID, including cancer (see "After COVID-19 Successes, Researchers Push to Develop mRNA Vaccines for Other Diseases"). Here's to your long and healthy life.

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Health & Medicine

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On the Cover

New research pins the maximum length of human life

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Humans Could Live up to 150 Years, New Research Suggests

A study counts blood cells and footsteps to predict a hard limit to our longevity

The chorus of the theme song for the movie *Fame*, performed by actress Irene Cara, includes the line "I'm gonna live forever." Cara was, of course, singing about the posthumous longevity that fame can confer. But a literal expression of this hubris resonates in some corners of the world—especially in the technology industry. In Silicon Valley, immortality is sometimes elevated to the status of a corporeal goal. Plenty of big names in big tech have sunk funding into ventures to solve the problem of death as if it were just an upgrade to your smartphone's operating system.

Yet what if death simply cannot be

Jeanne Calment enjoys her daily cigarette and glass of red wine on the occasion of her 117th birthday. In 1997 she died at the age of 122 and still holds the record for being the person with the longest lifespan.

Jean-Pierre Fizet *Getty Images*

hacked and longevity will always have a ceiling, no matter what we do? Researchers have now taken on the question of how long we can live if, by some combination of serendipity and genetics, we do not die from cancer, heart disease or getting hit by a bus. They report that when omitting things that usually kill us, our body's capacity to restore equilibrium to its myriad structural and metabolic systems after disruptions still fades with time. And even if we make it through life with few stressors, this incremental decline sets the maximum life span for humans at somewhere between 120 and 150 years. In the end, if the obvious hazards do not take our lives, this fundamental loss of resilience will do so, the researchers conclude in findings published on May 25 in *Nature Communications*.

"They are asking the question of 'What's the longest life that could be lived by a human complex system if everything else went really well and it's in a stressor-free environment?'" says Heather Whitson, director of the Duke University Center for the Study of Aging and Human Development, who was not involved in the paper. The team's results point to an underlying "pace of aging" that sets the limits on life span, she says.

For the study, Timothy Pyrkov, a researcher at a Singapore-based company called Gero, and his colleagues looked at this "pace of aging" in three large cohorts in the U.S., the U.K. and Russia. To evaluate deviations from stable health, they assessed changes in blood cell counts and the daily number of steps taken and analyzed them by age groups.

For both blood cell and step counts, the pattern was the same: as age increased, some factor beyond disease drove a predictable and incremental decline in the body's ability to return blood cells or gait to a stable level after a disruption. When Pyrkov and his colleagues in Moscow and Buffalo, N.Y., used this predictable pace of decline to determine when resilience would disappear entirely, leading to death, they found a range of 120 to 150 years. (In 1997 Jeanne Calment, the oldest person on record to have ever lived, died in France at the age of 122.)

The researchers also found that with age, the body's response to insults could increasingly range far from a stable normal, requiring more time for recovery. Whitson says that this result makes sense: A healthy young person can produce a rapid physiological response to adjust to fluctuations and restore a personal norm. But in an older person, she says, "everything is just a little bit dampened, a little slower to respond, and you can get overshoots," such as when an illness brings on big swings in blood pressure.

Measurements such as blood pressure and blood cell counts have a known healthy range, however, Whitson points out, whereas step counts are highly personal. The fact that Pyrkov and his colleagues chose a variable that is so different from blood counts and still discovered the same decline over time may suggest a real pace-of-aging factor in play across different domains.

Study co-author Peter Fedichev, who trained as a physicist and co-founded Gero, says that although most biologists would view blood cell counts and step counts as "pretty different," the fact that both sources "paint exactly the same future" suggests that this pace-of-aging component is real.

The authors pointed to social factors that reflect the findings. "We observed a steep turn at about the age of 35 to 40 years that was quite surprising," Pyrkov says. For example, he notes, this period is often a time when an athlete's sports career ends, "an indication that something in physiology may really be changing at this age."

The desire to unlock the secrets of immortality has likely been around as long as humans' awareness of death. But a long life span is not the same as a long health span, says S. Jay Olshansky, a professor of epidemiology and biostatistics at the University of Illinois at Chicago, who was not involved in the work. "The focus shouldn't be on living longer but on living healthier longer," he says.

"Death is not the only thing that matters," Whitson says. "Other things, like quality of life, start mattering more and more as people experience the loss of them." The death modeled in this study, she says, "is the ultimate lingering death. And the question is: Can we extend life without also extending the proportion of time that people go through a frail state?"

The researchers' "final conclusion is interesting to see," Olshansky says. He characterizes it as "Hey, guess what? Treating diseases in the long run is not going to have the effect that you might want it to have. These

fundamental biological processes of aging are going to continue."

The idea of slowing down the aging process has drawn attention, not just from Silicon Valley types who dream about uploading their memories to computers but also from a cadre of researchers who view such interventions as a means to "compress morbidity"—to diminish illness and infirmity at the end of life to extend health span. The question of whether this will have any impact on the fundamental upper limits identified in the *Nature Communications* paper remains highly speculative. But some studies are being launched—testing the diabetes drug metformin, for example—with the goal of attenuating hallmark indicators of aging.

In this same vein, Fedichev and his team are not discouraged by their estimates of maximum human life span. His view is that their research marks the beginning of a longer journey. "Measuring something is the first step before producing an intervention," Fedichev says. As he puts it, the next steps, now that the team has measured this independent pace of aging, will be to find ways to "intercept the loss of resilience."

—Emily Willingham

Mix-and-Match COVID Vaccines Trigger Potent Immune Response

Preliminary results from a trial of more than 600 people are the first to show the benefits of combining different vaccines

Vaccinating people with both the Oxford-AstraZeneca and Pfizer-BioNTech COVID-19 vaccines produces a potent immune response against the virus SARS-CoV-2, researchers conducting a study in Spain have found.

Preliminary results from the trial of more than 600 people—announced in an online presentation on May 18—are the first to show the benefits of combining different coronavirus vaccines. A U.K. trial of a similar strategy reported safety data in May and is expected to deliver further findings on immune responses soon.

Because of safety concerns, several European countries are already recommending that some or all people who were given a first dose of the vaccine developed by the University of Oxford and AstraZeneca get another vaccine for their second dose. Researchers hope that such mix-and-match COVID-19 vaccination regimens will trigger stronger, more robust immune responses than will two doses of a single vaccine, while simplifying immunization efforts for countries facing fluctuating supplies of the various vaccines.

Countries with fluctuating supplies of COVID-19 vaccines could benefit from using different vaccines for the first and second dose.

Christof Stache *Getty Images*

"It appears that the Pfizer vaccine boosted antibody responses remarkably in one-dose AstraZeneca vaccinees. This is all around wonderful news," says Zhou Xing, an immunologist at McMaster University in Hamilton, Canada.

PRIME AND BOOST

Starting in April, the Spanish Combi-

vacS trial enrolled 663 people who had already received a first dose of the Oxford-AstraZeneca vaccine, which uses a harmless chimpanzee adenovirus to deliver instructions for cells to make a SARS-CoV-2 protein. Two thirds of participants were randomly picked to receive the mRNA-based vaccine made by Pfizer, based in New York City, and BioNTech, in Mainz, Germany, at least eight weeks after their first dose. A control group of 232 people has not yet received a booster. The study was led by the Carlos III Health Institute in Madrid.

The Pfizer-BioNTech booster seemed to jolt the immune systems of the Oxford-AstraZeneca-dosed participants, reported Magdalena Campins, an investigator on the CombivacS study at Vall d'Hebron University Hospital in Barcelona. After this second dose, participants began to produce much higher levels of antibodies than they did before, and these antibodies were able to recognize and inactivate SARS-CoV-2 in laboratory tests. Control participants who did not receive a booster vaccination experienced no change in antibody levels.

That is what researchers hoped for and expected from mixing different vaccines, a strategy known as a heterologous prime and boost, which has been deployed for vaccines against other diseases, such as Ebola. "These responses look promising and show the potential of heterologous prime-boost regimens," says Dan Barouch, director of the Center for Virology and Vaccine Research at Beth Israel Deaconess Medical Center in Boston.

Xing says the antibody response to the Pfizer boost seems to be even stronger than the one most people generate after receiving two doses of the Oxford-AstraZeneca vaccine, according to earlier trial data. But it is not clear how those responses compare with those seen in people who receive two doses of mRNA vaccines such as Pfizer-BioNTech's, which tend to trigger an especially potent antibody response after a second dose.

Making such comparisons is "apples and oranges," says Daniel Altmann, an immunologist at Imperial College London. A strong immune response to the mix-and-match strategy is "entirely predictable from the basic immunology," he adds.

Giving people first and second doses of different vaccines probably makes sense, Altmann says. But he wonders what will happen if people need a third dose to prolong immunity or protect against emerging coronavirus variants. Repeated doses of virus-based vaccines such as the Oxford-AstraZeneca one tend to be increasingly less effective because the immune system mounts a response against the adenovirus. RNA vaccines, in contrast, tend to trigger stronger side effects with added doses. "I do think there's a brave new world of vaccinology to be scoped in all of this," Altmann says.

In May, a U.K. study called Com-COV, which analyzed combinations of the same two vaccines, found that people in the mix-and-match groups experienced higher rates of common vaccine-related side effects, such as fever, than did people who received two doses of the same vaccine. In the Spanish CombivacS trial, mild side effects were common and similar to those seen in standard COVID-19 vaccine regimens. None was deemed severe.

—Ewen Callaway

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Limit on Lab-Grown Human Embryos Dropped by Stem Cell Body

The International Society for Stem Cell Research relaxed the famous 14-day rule on culturing human embryos in its latest research guidelines

The international body representing stem cell scientists has torn up a decades-old limit on the length of time that scientists should grow human embryos in the laboratory, giving more leeway to researchers who are studying human development and disease.

Previously, the International Society for Stem Cell Research (ISSCR) recommended that scientists culture human embryos for no more than two weeks after fertilization. But on May 26, the society said it was relaxing this famous limit, known as the 14-day rule. Rather than replacing or extending the limit, the ISSCR now suggests that studies proposing to grow human embryos beyond the two-week mark

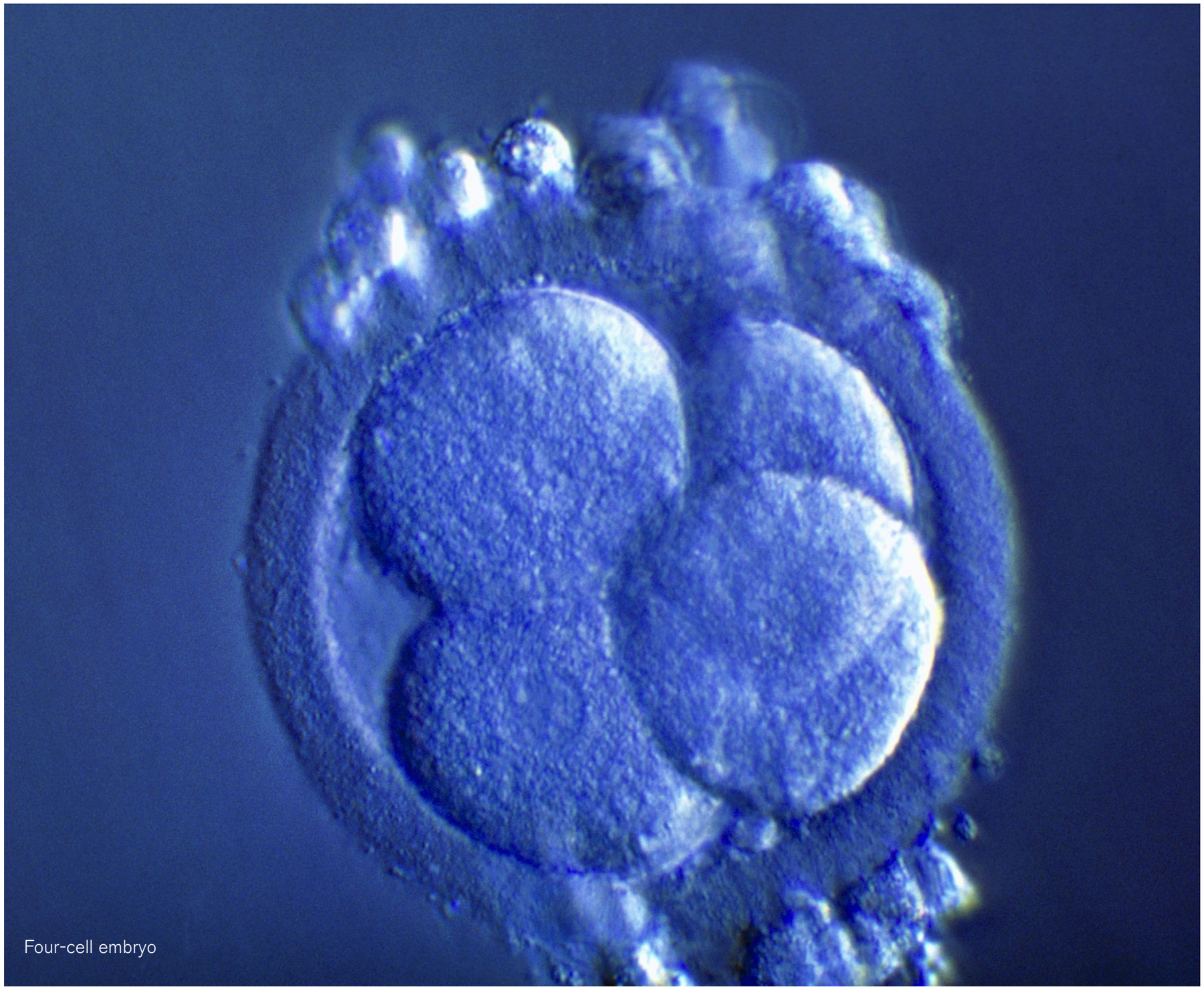
be considered on a case-by-case basis and be subjected to several phases of review to determine at what point the experiments must be stopped.

The ISSCR made this change and others to its guidelines for biomedical research in response to rapid advances in the field, including the ability to create embryolike structures from human stem cells. In addition to relaxing the 14-day rule, for instance, the group advises against editing genes in human embryos until the safety of genome editing is better established.

"It's been a major revision," says Robin Lovell-Badge, a stem cell biologist at the Francis Crick Institute in London and chair of the ISSCR steering committee that wrote the new guidelines.

Last revised in 2016, the document offers a rubric for what science the biomedical community agrees is worthy and which projects are off-limits.

In the U.S., where biomedical research involving stem cells or human embryos has been controversial for decades and federal support has waxed and waned, the guidelines carry unusual weight, says Josephine Johnston, a bioethicist at



Four-cell embryo

Pascal Goetgheluck *Science Source*

the Hastings Center in Garrison, N.Y. Although U.S. agencies have some policies covering such work, review committees at institutions or private funders often turn to the ISSCR's document as the only regularly updated set of guidelines representing the views of the scientific community. "That means that when they make a change like this, it is actually fairly significant," Johnston says.

THE 14-DAY RULE

First proposed in 1979, the 14-day rule bars research on embryos after they reach a key point of complexity. At least a dozen countries, including the U.K., Canada and South Korea, have adopted the concept as law. Others, including the U.S., have accepted it as a standard that guides researchers, reviewers and regulators.

With the new ISSCR recommmendations, Lovell-Badge envisions that the longer a researcher wants to culture an embryo for, the tougher the review process by a country's regulatory authorities would be. "We're not simply giving green lights for people to do this research," he says. Furthermore, the guidelines say public comment should be part of the review.

Before 2016, researchers were not able to keep human embryos alive in a dish for 14 days, so the rule did not bar any projects. But that year, two independent research teams announced that they had been able to grow human embryos in a dish for up to 13 days—they then terminated the experiments in accordance with the 14-day standard.

Such advances have led some ethicists and researchers to argue that the decades-old rule is antiquated and ripe for revision. Allowing embryos to grow past 14 days, researchers say, could produce a better understanding of human development and enable scientists to learn why some pregnancies fail, for instance. The revised ISSCR guidelines are a prompt to begin conversations about when it would be valuable to grow embryos beyond 14 days, says Alta Charo, a bioethicist at the University of Wisconsin Law School in Madison, who was part of the ISSCR steering committee. "We didn't debate it before—now it's time to debate."

Aryeh Warmflash, a stem cell biologist at Rice University, believes weighing research benefits against ethical questions on a case-by-case basis, experiment by experiment, is an effective step—although he says he would eventually like to see more guidance on how to evaluate those trade-offs. But "it was a good choice not to frame this around advocating another 'X-day' rule," he wrote in an e-mail to *Nature*.

STEM CELL MODEL

In the past decade scientists have made increasingly sophisticated models of embryos from human stem cells, demonstrating one way to study human development while avoiding the controversial use of embryos from fertility clinics. Such embryolike structures are too rudimentary to grow into a person, scientists say. But relaxing the 14-day limit would allow researchers to compare them fully with real embryos and test them as feasible stand-ins for research, Lovell-Badge says. Although the embryolike structures are not technically bound by the 14-day rule, some scientists have said that they observe the limit when growing the model systems because they are uncertain about the community consensus.

The relaxation of the 14-day rule "is really significant, but it's done with a soft touch," Johnston says.

Not everyone agrees that the shift is justified. Kirstin Matthews, a legal and policy scholar at Rice University's Baker Institute for Public Policy, says that there is unexplored science to be done with embryos that are two weeks or younger and that given the public scrutiny of studies of human embryos, the ISSCR should have engaged the public while considering changes to the guidelines. "It doesn't feel like we've exhausted our knowledge in this space," she says.

Lovell-Badge acknowledges that the review and redrafting steps did not include public-engagement exercises, in part because of the cost and time involved. Also, an international public-comment period would probably receive varied responses from different jurisdictions, he says. "You'd have to make it a huge exercise, and we can't do that."

SHIFTS IN GENETIC SCIENCE

Some of the other key changes to the ISSCR's ethics guide reflect advances in genetics.

For example, the guidelines now describe terms under which mitochondrial-replacement therapy could

be used in medical research. Some metabolic diseases are caused by genetic mutations in the mitochondria, the power generators in cells, which children receive from their mothers. In cases where a mother's mitochondria carry these mutations, doctors can now swap the nucleus from the mother's egg cell into a donor cell with healthy mitochondria, whose nucleus has been removed, before in vitro fertilization (IVF). A baby born as a result of this technique would have mitochondrial genes from the donor, but their nuclear DNA would come from the mother and from the father whose sperm is used in IVF.

In 2016 U.S. physician John Zhang announced that he had attempted such a procedure and delivered in Mexico what news reports called a three-parent baby. At the time, some researchers worried that the country was chosen for its lax regulations. Since then, researchers in the U.K. have won approval to begin clinical trials of the method. In the U.S., a clause in the annual budget legislation prohibits the Food and Drug Administration from considering such a technique. But Johnston says that might change soon: "I would be very surprised if it stays."

The ISSCR guide also weighs in on whether it is okay to edit the genes of human embryos or egg or sperm cells intended for implantation and concludes that this science is still too risky. In 2018 scientists were alarmed by an announcement from Chinese biophysicist He Jiankui that he had used CRISPR-Cas9 technology to edit genes in human embryos that he then implanted in a woman's uterus, resulting in the birth of twin girls. Since then, other expert panels have debated how to regulate gene editing that introduces heritable changes. They have pointed out that the procedure, still fairly nascent, can cause unintended changes to genes and has other technical flaws.

The ISSCR allows that the concept might be valuable in the future, for scientifically defensible reasons, once the science has advanced and after extensive review. "As a matter of absolute principle, we do not say that heritable editing is absolutely wrong in every possible circumstance," Charo says.

—Nidhi Subbaraman

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Why Deadly "Black Fungus" Is Ravaging COVID Patients in India

Standard treatments such as steroids, as well as illnesses such as diabetes, make the fungal infection worse

The hospital of the Mahatma Gandhi Institute of Medical Sciences, a medical school in the town of Sevagram in the Indian state of Maharashtra, has been taking in patients afflicted with COVID since May 2020. But in the middle of April 2021, something changed. Patients arrived with problems the physicians there had not yet seen in the pandemic: people were not only breathless and feverish yet had pain and pressure behind their cheekbones and around their eyes.

Their cases were some of the earliest indications of a wave of illness that is now swamping India, an epidemic within the pandemic: infections with a rare group of fungi called mucormycetes. The infection they cause, mucormycosis—"black fungus," colloquially—can infest the sinuses and bones of the face and invade the brain or cause patients to lose an eye. When it goes untreated—and treatment is prolonged and difficult—mucormycosis can kill up to half of those who contract it.

There have been almost 12,000 cases of the infection in India in recent months, with most of them occurring in the western states of Maharashtra and Gujarat. "There was no fungus in the first wave" of COVID, says S. P. Kalantri, a professor of medicine at the Mahatma Gandhi Institute of Medical Sciences and medical superintendent of its hospital. "The black fungus has painted the country red in the second wave."

The epidemic of mucormycosis is yet another of the unpleasant surprises produced by the COVID pandemic—following MIS-C, a severe inflammatory syndrome that seems to mostly affect children, and "long COVID," a complex of symptoms that continue to afflict patients months after initial infection. Mucormycosis is one of an array of ferocious fungal diseases that have attacked COVID patients, including a lethal yeast called *Candida auris* and a spate of infections with *Aspergillus* fungi

Doctor examines a patient with "black fungus," a deadly infection, at a civil hospital in Ahmadabad, India.

Sam Panthaky *Getty Images*

that have earned the acronym CAPA (for COVID-associated pulmonary aspergillosis).

These fungal infections arise after a COVID diagnosis, which seems to be a clue. A standard component of treatment for severe cases of COVID is high doses of corticosteroids, anti-inflammatory drugs that damp down the immune system's overreaction to infection. Steroids save lives, but they simultaneously make a patient more vulnerable to attack by whatever bacteria or fungi are already in their body or hanging around their environment.

"Fungal spores are everywhere, but we are pretty efficient at clearing them from our lungs," says Arturo Casadevall, a physician and molecular microbiologist at the Johns Hopkins Bloomberg School of Public Health. "But COVID damages the lung. So then you have a double whammy: reduced capacity to naturally clear the spores and reduced immune response as a result of steroids."

That collision of factors is complicated by something else. Years before COVID appeared, researchers in Australia and Europe, as well as India, all reported that mucormycosis seemed particularly ferocious in patients with uncontrolled diabetes. That is setting Indian COVID patients up for disaster. "Even in rural areas, every eighth adult aged 30 and beyond is diabetic," Kalantri says. "Most have suboptimal control of sugar. When these patients test COVID-positive, they often are prescribed high-dose steroids, often in the first week. Irrational and unscientific treatment of COVID is extremely common."

Fungal infections after COVID have been so widely reported from multiple countries that physicians are starting to develop treatment algorithms to blunt their attack. "People who present with COVID and a new diabetes diagnosis or severe diabetes—that is an extreme risk," says Kieren Marr, a physician at the Johns Hopkins University School of Medicine and medical director of its transplant and oncology infectious diseases program, who recently published research on *Aspergillus* fungus infections in COVID patients. "In our center, we would say that all of the risk factors would justify potentially giving an antifungal drug preventively."

Identifying a case of mucormycosis early can be challenging. Unlike some other fungal infections, there are no blood-based tests that can detect it. Diagnosis requires doing a biopsy, examining the sample and sometimes following up with a CT scan—all of which imply the availability of specialty personnel to perform those tasks and advanced

equipment to support them. In the underresourced parts of India's vast health-care system, those cannot be guaranteed.

Even antifungal drugs are in short supply in India, according to news reports, and they may be unaffordable for most. There are relatively few categories of antifungals, and while some of them have been available for decades, newer versions that are less toxic to patients are expensive and scarce. For the preferred drug, "one-day therapy costs 30,000 rupees (about $410), a catastrophic health expenditure for 99 percent of Indians," Kalantri says. "The therapy often lasts for weeks and requires an intravenous infusion, admission to the hospital and close monitoring of kidney function."

It is not possible, at this point, to predict an end to the shadow epidemic of black fungus, although greater awareness of patients' vulnerability may allow physicians in India to recognize cases earlier. For now, it remains one more way in which the pandemic caught the world by surprise and one more illustration of how its worst effects have fallen hardest on countries that can afford them least. —*Maryn McKenna*

Injection of Light-Sensitive Proteins Restores Blind Man's Vision

The first successful clinical test of optogenetics lets a person see for the first time in decades, with help from image-enhancing goggles

Carmelo Geraci *Getty Images*

After 40 years of blindness, a 58-year-old man can once again see images and moving objects, thanks to an injection of light-sensitive proteins into his retina.

The study, published on May 24 in *Nature Medicine*, is the first successful clinical application of a technique called optogenetics, which uses flashes of light to control gene expression and neuron firing. The technique is widely used in laboratories to probe neural circuitry and is being investigated as a potential treatment for pain, blindness and brain disorders.

The clinical trial, run by the company GenSight Biologics, headquartered in Paris, enrolls people with retinitis pigmentosa (RP): a degenerative disease that kills off the eye's photoreceptor cells, which are the first step in the visual pathway. In a healthy retina, photoreceptors detect light and send electrical signals to retinal ganglion cells (RGCs), which then transmit the signal to the brain. GenSight's optogenetic therapy skips the damaged photoreceptor cells entirely by using a virus to deliver light-sensitive bacterial proteins into the RGCs, allowing them to detect images directly.

The researchers injected the virus into the eye of a man with RP, then waited four months for the RGCs to begin producing the proteins before testing his vision. Ophthalmologist José-Alain Sahel of the University of Pittsburgh Medical Center, who led the study, says one of the challenges was regulating the amount and type of light entering the eye because a healthy retina uses a variety of cells and light-sensitive proteins to see a wide range of light. "No protein can replicate what the system can do," he says. So the researchers engineered a set of goggles that capture the

images around the man and optimize them for detection by the bacterial proteins.

Using a camera, the goggles analyze changes in contrast and brightness and convert them in real time into what Sahel describes as a "starry sky" of amber-colored dots. When the light from these dots enters a person's eye, it activates the proteins and causes the RGCs to send a signal to the brain, which then resolves these patterns into an image.

The man taking part in the trial had to train with the goggles for several months before his brain adjusted to interpret the dots correctly. "He was like an experimentalist, a scientist trying to understand what he was seeing and make sense of it," Sahel says. Eventually he was able to make out high-contrast images, including objects on a table and the white stripes in a crosswalk. When the researchers recorded his brain activity, they found that his visual cortex reacted to the image in the same way as it would if he had normal sight.

The man still can't see without the goggles, but Sahel says that he wears them for several hours per day and that his vision has continued to improve in the two years since his injection. Six other people were injected with the same light-sensitive proteins last year, but the COVID-19 epidemic delayed their training with the goggles. Sahel says he expects to have their results within about a year.

SAFE AND PERMANENT

"It's a big step for the field," says John Flannery, a neurobiologist at the University of California, Berkeley. "The most important thing is that it seems to be safe and permanent, which is really encouraging." Because the retina contains around 100 times more photoreceptors than RGCs, the resolution of images detected by RGCs will never be as good as natural vision. But Flannery says it is exciting that the brain can interpret images accurately.

Others say that more research is needed. "It's interesting, but it's an N of 1," says Sheila Nirenberg, a neuroscientist at Weill Cornell Medical College in New York City. She adds that she looks forward to seeing whether the other people in the trial, including some who were injected with higher doses of the protein, have similar results.

GenSight is one of several companies developing optogenetics as a treatment for RP and other disorders of the retina. In March, Nirenberg's company Bionic Sight announced that four of the five people with RP it treated with a similar optogenetic therapy and a virtual-reality headset had recovered some level of vision, although the full trial results have not yet been published. And Swiss pharma giant Novartis is developing a therapy based on a different protein that is so light-sensitive that goggles may not be needed. That therapy has not yet entered clinical trials.

Neuroscientist Karl Deisseroth of Stanford University, who co-developed optogenetics as a laboratory technique, says the study is important because it is the first time that its effects have been shown in people. "It will be interesting to try this with more light-sensitive opsins" that might not require goggles, he says. But he expects optogenetics to be most useful as a research tool that leads to therapies rather than a therapy itself. "What we hope to see even more of is optogenetics-guided human and clinical studies," he says.

—Sara Reardon

This article is reproduced with permission and was first published in Nature *on May 24, 2021.*

Flu Has Disappeared Worldwide during the COVID Pandemic

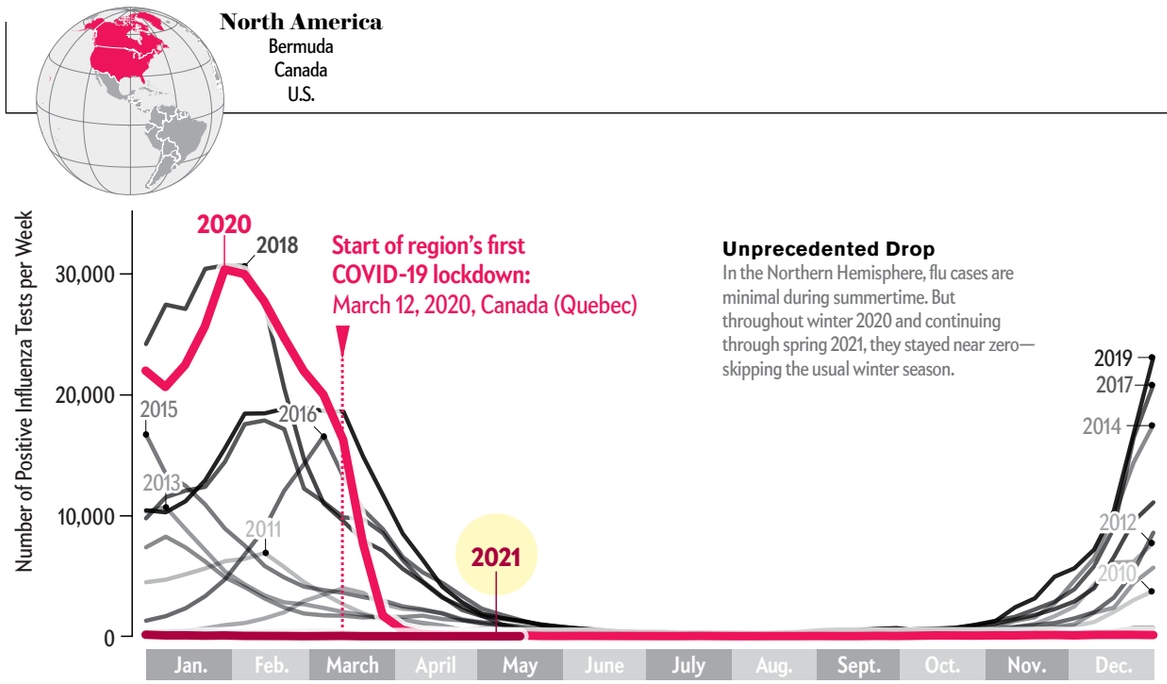
The public health measures that slow the spread of the novel coronavirus work really well on influenza

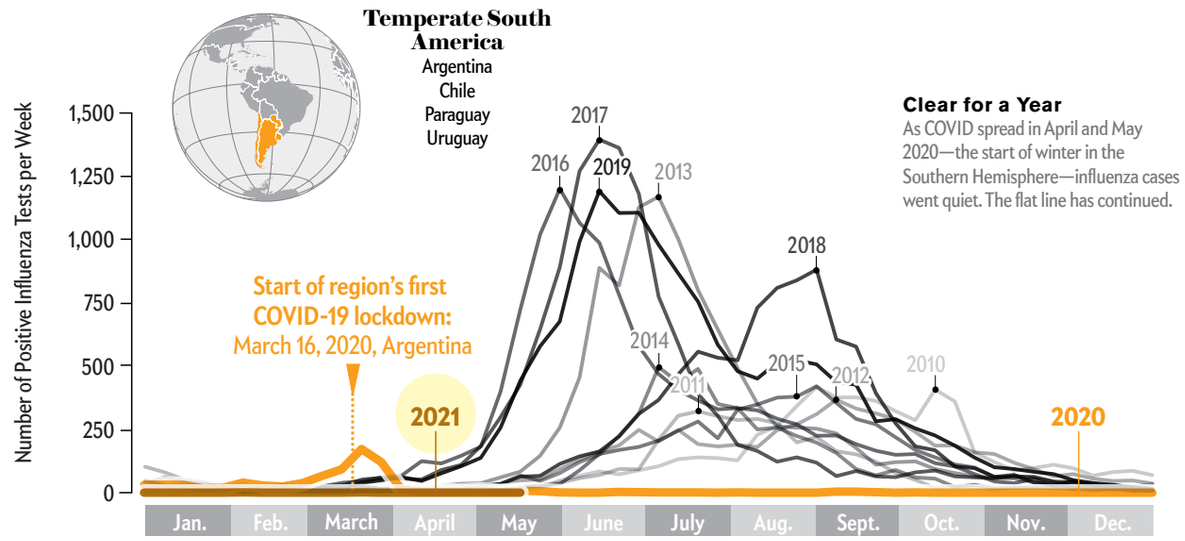
Since the novel coronavirus began its global spread, influenza cases reported to the World Health Organization have dropped to minuscule levels. The reason, epidemiologists think, is that the public health measures taken to keep the coronavirus from spreading also stop the flu. Influenza viruses are transmitted in much the same way as SARS-CoV-2, but they are less effective at jumping from host to host.

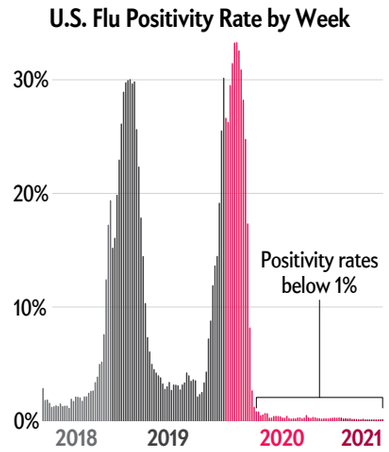
As *Scientific American* reported last fall, the drop-off in flu numbers was both swift and universal. Since then, cases have stayed remarkably low. "There's just no flu circulating," says Greg Poland, who has studied the disease at the Mayo Clinic for decades. The U.S. saw about 600 deaths from influenza during the 2020–2021 flu season. In compari-

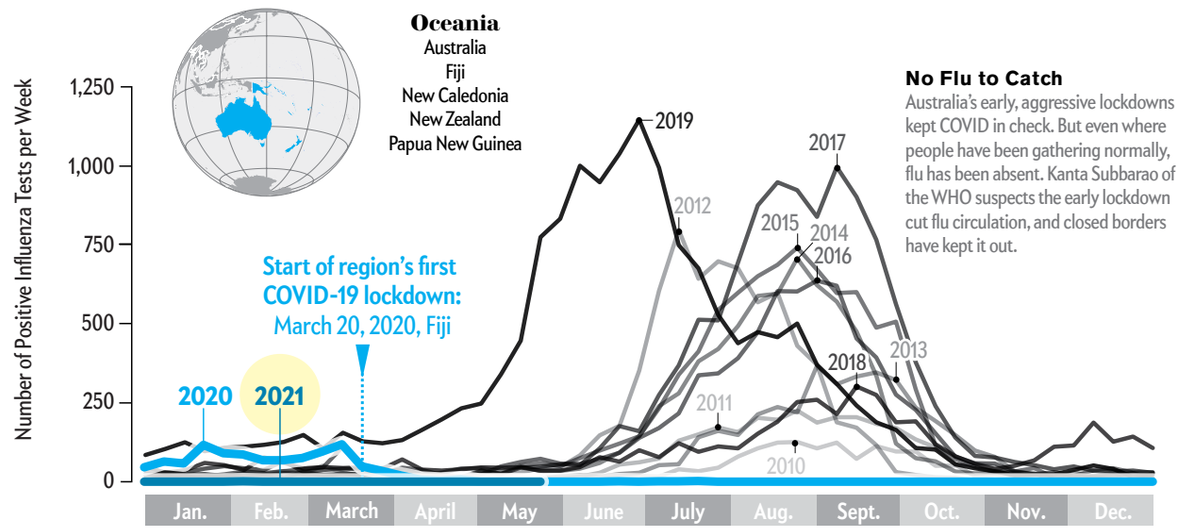
Influenza Cases Worldwide, by Region

The World Health Organization tracks influenza transmission in 18 zones. Three of those regions appear here. Only people who get tested for influenzalike illnesses—typically about 5 percent of individuals who fall ill—are tallied.









son, the Centers for Disease Control and Prevention estimated there were roughly 22,000 deaths in the prior season and 34,000 two seasons ago.

Because each year's flu vaccine is based on strains that have been circulating during the past year, it is unclear how next year's vaccine will fare, should the typical patterns of the disease return. The WHO made its flu strain recommendations for vaccines in late February as usual, but they were based on far fewer cases than in a common year. At the same time, with fewer virus particles circulating in the world, there is less chance of an upcoming mutation, so it is possible the 2021–2022 vaccine will prove extra effective.

Public health experts are grateful for the reprieve. Some are also worried about a lost immune response, however. If influenza subsides for several years, today's toddlers could miss a chance to have an early-age response imprinted on their immune system. That could be good or bad, depending on what strains circulate during the rest of their life. For now, future flu transmission remains a roll of the dice.

— Katie Peek

Katie Peek

Six Months of COVID Vaccines: What 1.7 Billion Doses Have Taught Scientists

At a pivotal moment in the pandemic, *Nature* explores key questions about the vaccines that countries are racing to deliver while viral variants spread around the globe *By Heidi Ledford*

A campaign to vaccinate people against COVID-19 in Goma, Democratic Republic of the Congo, in May.

Guerchom Ndebo *Getty Images*

Heidi Ledford works for *Nature* magazine.

OVER THE PAST SIX MONTHS, HUNDREDS of millions of people around the world have rushed to follow in the footsteps of a 90-year-old British woman named Margaret Keenan. At 6:30 A.M. on December 8, 2020, Keenan became the first person to receive a COVID-19 vaccine as part of a mass vaccination effort. Her shot was the culmination of a frenzied effort to develop vaccines safely and in record time. Now, more than 1.7 billion doses later, researchers are sifting through the data to address lingering questions about how well the vaccines work—and how they might shape the course of the coronavirus pandemic that has already taken more than 3.5 million lives.

"It's absolutely astonishing that this has happened in such a short time—to me, it's equivalent to putting a person on the moon," says pediatric infectious disease specialist Cody Meissner at the Tufts University School of Medicine and Tufts Children's Hospital in Boston. "This is going to change vaccinology forever."

Nature looks at what lessons have emerged during the first six months of COVID-19 vaccinations, as well as what questions still linger. Overall, the vaccine results have been extremely promising—even better than many had hoped—but researchers have concerns about emerging variants and the potential for immune responses to wane.

HOW WELL DO THE VACCINES WORK IN THE REAL WORLD?

Danish epidemiologist Ida Moustsen-Helms was excited in February when she first saw how well the Pfizer-BioNTech vaccine was working in health-care workers and residents of long-term-care facilities, who were the first to receive it in Denmark. A clinical trial in more than 40,000 people had already found the vaccine to be 95 percent effective in protecting recipients from symptomatic COVID-19. But Moustsen-Helms, who works at the Statens Serum Institute in Copenhagen, and her colleagues were among the first to test its effectiveness outside clinical trials, which can exclude some unhealthy individuals or those taking medicines that suppress immune responses.

The results showed it was 64 percent effective in long-term-care residents with a median age of 84 and 90 percent effective in health care workers—which struck Moustsen-Helms as good news, given that immune responses in older people can be muted. But some Danish politicians were upset by the relatively low effectiveness in older recipients. "People were saying, 'How can this be true?'" she says. "Sometimes they forget that when you look at a trial result, those individuals included in trials are very different from people in the real world."

Since then, real-world data have come in from several countries, and much of the news has continued to be positive about how well vaccines perform in the general population. A nationwide vaccination campaign in Israel found the Pfizer-BioNTech vaccine, co-developed by Pfizer in New York City and BioNTech in Mainz, Germany, to be 95 percent effective against SARS-CoV-2 infection seven days or more after the second dose. The Gamaleya National Research Center of Epidemiology and Microbiology in Moscow and the Russian Direct Investment Fund announced that their Sputnik V vaccine has been 97 percent effective in almost four million people in Russia. And in May, London-based Public Health England reported that the Pfizer-BioNTech and Oxford-AstraZeneca vaccines are both 85 to 90 percent effective in preventing symptomatic disease after two doses. It cautioned, however, that it had low statistical confidence in the result for

the Oxford-AstraZeneca jab, developed by the University of Oxford and by AstraZeneca in Cambridge, England.

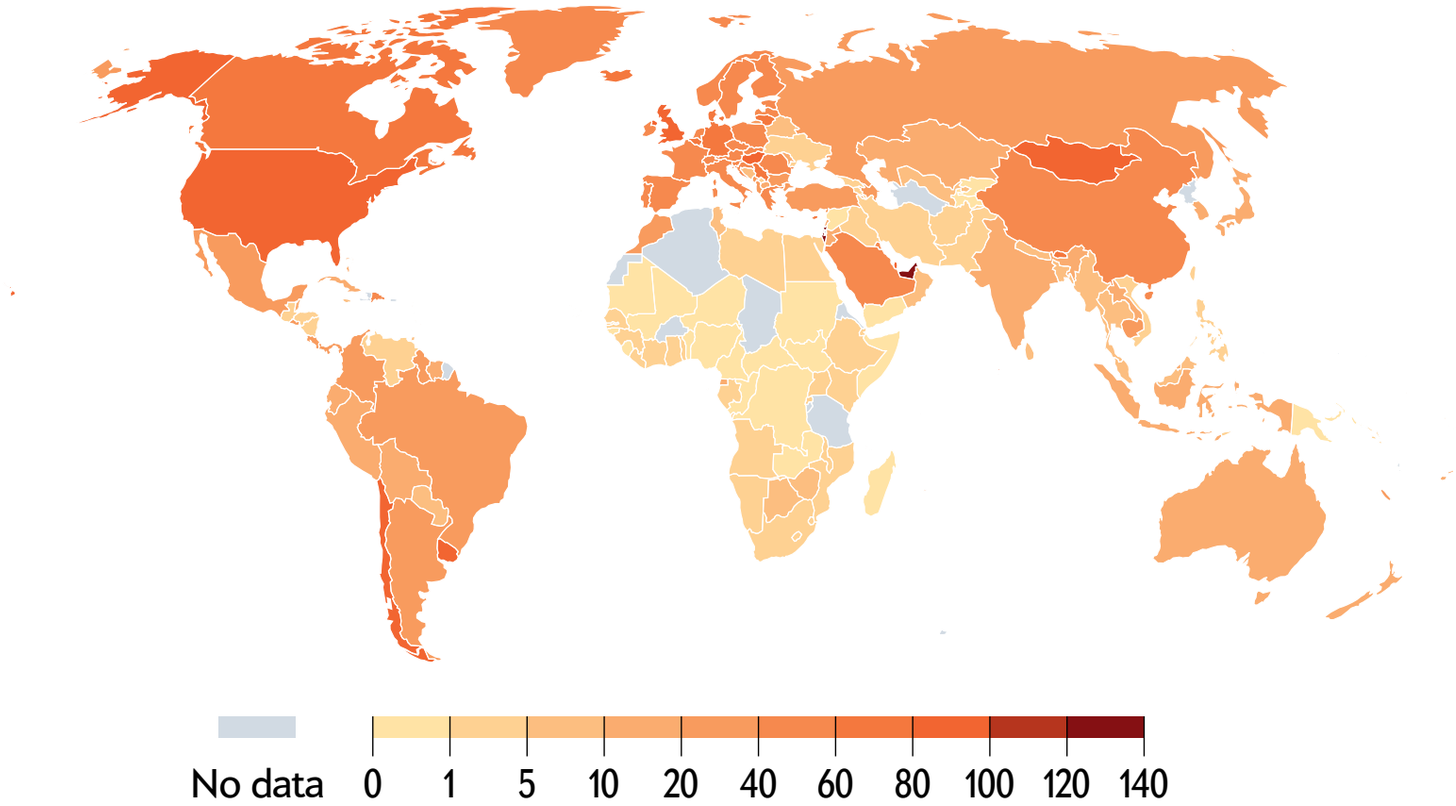
Among older adults who received the Pfizer-BioNTech vaccine, Israel has seen 94 percent protection from SARS-CoV-2 infection in people older than 85 years. This is remarkably high for that age group and considerably higher than Moustsen-Helms's result of 64 percent, possibly in part because long-term-care residents are prone to be in poor health. Similarly, a U.K. study found that the Pfizer-BioNTech and Oxford-AstraZeneca vaccines were both 80 percent effective at preventing COVID-19 hospitalizations in people aged 70 or older. Studies are underway to see whether vaccine effectiveness can be boosted even more by mixing and matching vaccines, and early results have been promising.

But the vaccines have already exceeded expectations, Meissner says, especially given how quickly they were developed—despite thorough safety testing in unusually large clinical trials—and the novel approaches they used. Some vaccines spend years in development and still might not achieve this level of protection. "The efficacy of these vaccines is absolutely remarkable," Meissner says.

At the other end of the age spectrum, Pfizer-BioNTech and Moderna in Cambridge, Mass., have recently completed clinical trials of their vaccines in adolescents, showing 100 and 93 percent protection in those aged 12 to 15 and 12 to 17, respectively. Real-world data are not yet available. Meissner, who is an external adviser on vaccines to the U.S. Food and Drug Administration, questions whether children under 12 should get the vaccines before the shots have received full regulatory approval—rather than an emergency-use authorization.

Global Doses

Vaccine rollouts are uneven across the world, as shown by the number of COVID-19 vaccine doses administered per 100 people in the total population.*



*Data as of June 2, 2021. Data don't reflect the number of people who have been vaccinated because some people have received two doses of a vaccine. *Nature* publications remain neutral with regard to contested jurisdictional claims in published maps.

Nature; Source: *Our World in Data*

HOW EFFECTIVE ARE THE VACCINES AGAINST VARIANTS?

Soon after the triumph of Keenan's first dose, the world had a fresh reason to worry. A SARS-CoV-2 variant identified in the U.K. seemed to be spreading unusually fast; a different variant first identified in South Africa carried worrisome mutations in the coronavirus spike protein that serves as the basis for most COVID-19 vaccines in use.

Since then, further variants of concern have arrived in a steady parade, brandishing mutations that might boost the virus's spread or undermine the effectiveness of COVID-19 vaccines. "Uncontrolled outbreaks generate mutants," says Jerome Kim, director-general of the International Vaccine Institute in Seoul.

Initial laboratory tests suggested that antibodies raised by the Pfizer-BioNTech vaccine were less effective against the B.1.351 variant identified in South Africa, but it was unclear how that would affect protection against disease. In May, researchers in Qatar published reassuring data showing that people who received two doses of the Pfizer-BioNTech vaccine were 75 percent less likely

to develop COVID-19 from infection with B.1.351, and were almost completely protected from severe disease. "The big question right now is whether introduction of other variants could change the situation," says study author and infectious disease epidemiologist Laith Jamal Abu-Raddad of Weill Cornell Medicine–Qatar in Doha. "We are watching this on a daily basis, but we have optimism that maybe we have seen the worst."

The Oxford-AstraZeneca vaccine did not fare as well in another test: in South Africa, a small clinical trial suggested that the vaccine did little to fend off infections of the B.1.351 variant that, by that point, was causing most infections there. As a result, the South African government made the difficult decision to sell its doses and await a different vaccine. It is now rolling out the vaccine produced by Johnson & Johnson in New Brunswick, N.J., which in one clinical trial was 64 percent effective at blocking moderate to severe COVID-19 in South Africa at a time when B.1.351 constituted more than 94 percent of the infections in the trial. And a vaccine made by Novavax in Gaithersburg, Md., which has not yet been authorized for emergency use, was 51 percent effective at preventing symptomatic COVID-19 among participants in South Africa who did not have HIV.

But Shabir Madhi, an immunologist at the University of the Witwatersrand in Johannesburg and a lead investigator on trials of the vaccine in South Africa, disagreed with the country's decision not to use the Oxford-AstraZeneca vaccine. There was still hope that it could protect against severe disease and death, he says—a possibility that was not tested in the trial, which enrolled mostly young participants with a low risk of severe disease. Madhi notes that a later study in hamsters found that the vaccine prevented clinical disease caused by B.1.351.

The coronavirus SARS-CoV-2 has proved to be much more prone to mutations than researchers first thought, and more variants are emerging all the time. One variant of concern, called B.1.617.2, was first identified in India and is spreading rapidly in the U.K., raising worries that it could be unusually transmissible. Public Health England has determined that two doses of either the Pfizer-BioNTech or the Oxford-AstraZeneca vaccines are 88 nd 60 percent effective, respectively, at preventing symptomatic disease caused by this variant.

HOW LONG DOES PROTECTION AGAINST DISEASE LAST?

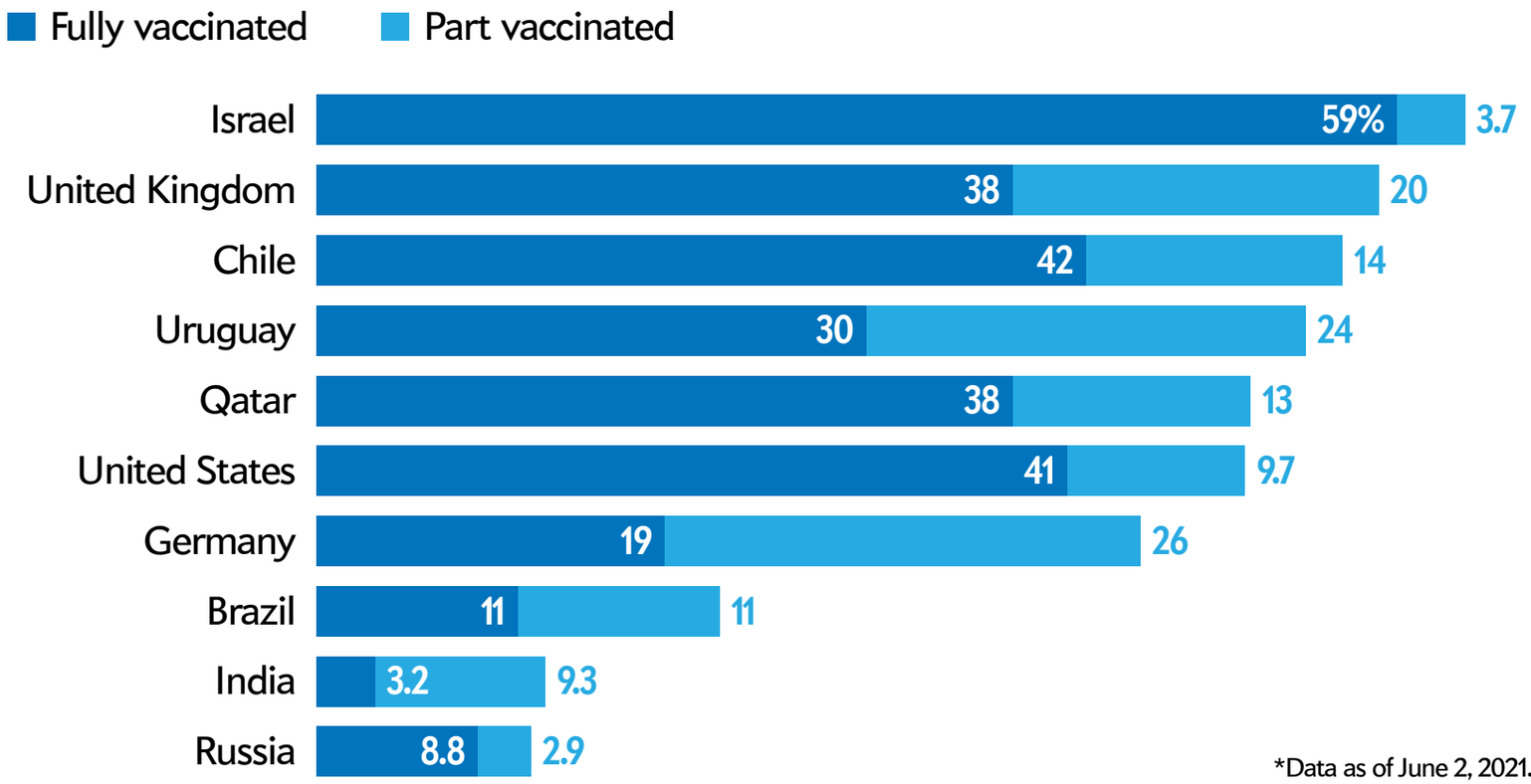
Six months is not much time to collect data on how durable vaccine responses will be, but data could soon emerge from clinical trial participants who had their first doses last July.

In the meantime, some researchers are looking to natural immunity as a guide. A study in more than 25,000 health-care workers in the U.K. found that a SARS-CoV-2 infection reduced the risk of catching the virus again by 84 percent for at least seven months. And Abu-Raddad says an unpublished study in Qatar is finding about 90 percent protection against reinfection as much as a year after a bout of SARS-CoV-2. "It seems to suggest that immunity is really strong against this virus," he says. "I'm optimistic that vaccine immunity is going to last more than a few months and longer than a year."

But Mehul Suthar, a viral immunologist at Emory

Vaccination Variation

Some countries have vaccinated more than half of their populations, whereas many nations lag behind because of difficulties in obtaining doses.*



*Data as of June 2, 2021.

Nature; Source: *Our World in Data*

University, is concerned that vaccine-induced immunity will not be as durable as immunity from natural infection. Suthar says that he and his collaborators have found that antibody levels declined faster in those who were vaccinated with the Moderna vaccine than in those who had been infected by SARS-CoV-2. Antibodies are not the only determinant of immunity, he says, but the results worry him. "I'm a little concerned that the vaccines weren't as robust in generating more durable antibody responses," Suthar says. "When you factor in variants, to me it's clear that we're going to need a booster."

How soon that booster is needed could depend in part on the rate at which antibody levels decline—they could drop precipitously or plateau at a low level. One modelling study estimates that low levels of antibodies will be enough to offer significant protection against severe disease. But Pfizer chief executive Albert Bourla has said that he expects a booster to be needed in about eight to 12 months after the second dose of the Pfizer-BioNTech vaccine.

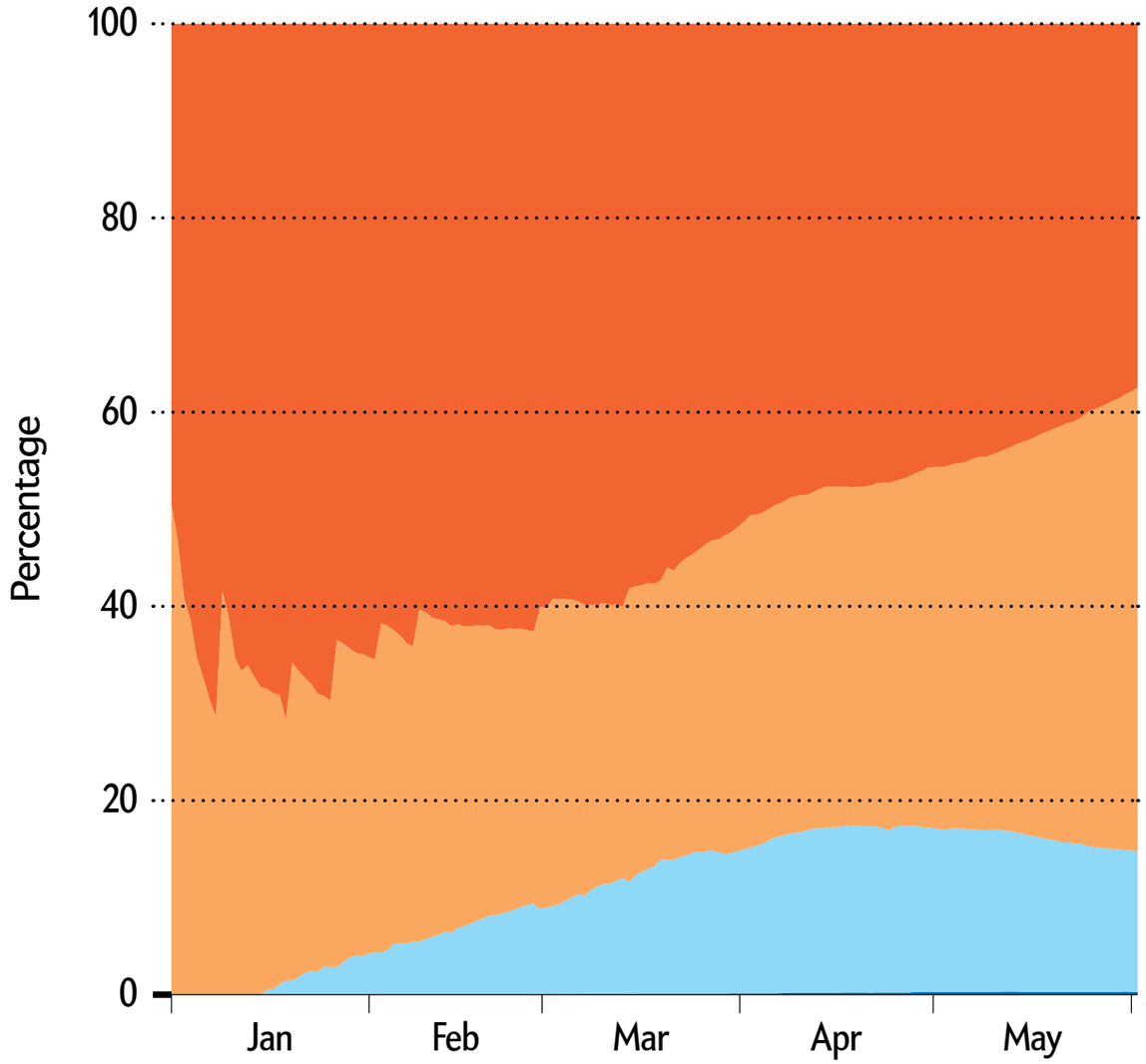
On May 19 the U.K. government announced that it had funded a study of seven different COVID-19 vaccines given as boosters at least 10 to 12 weeks after the second dose of an initial vaccine. Early findings are expected in September—in time to inform a booster program aimed at protecting the most vulnerable groups over the U.K. winter. The U.S. National Institutes of Health is also studying boosters in some study participants who received their first vaccine dose in an early clinical trial that began in March 2020.

Vaccine developers are now testing variant-specific boosters, too. Moderna has released preliminary results showing that a booster vaccine using a spike-protein sequence from the B.1.351 variant increased the concentration of antibodies that neutralize SARS-CoV-2, in particular the B.1.351 variant.

Even if immunity does fade earlier than he hopes, Abu-Raddad is optimistic that it won't disappear entirely. "If I would make a bet right now, I would say that even when people start losing their immunity against infection, they will not lose immunity against severe infections," he says.

Unequal Protection

Wealthier nations have secured an inordinate share of vaccine supplies, as seen in a graph showing the proportion of doses administered since January 2021.*



*Data as of June 2, 2021.

HOW MUCH DO VACCINES BLOCK TRANSMISSION?

Key clinical trials for currently authorized vaccines determined whether the inoculations could safely avert symptomatic disease in individuals. But blocking transmission of the virus is also crucial for ending a pandemic, and most of those clinical trials did not track asymptomatic infections that could fuel the virus's spread.

Researchers have been trying to fill this gap, and so far the data look promising. Results announced by Johnson & Johnson from clinical trials suggest that its vaccine is 74 percent effective against asymptomatic infections. Researchers studying deployment of the Pfizer-BioNTech vaccine in Israel have also reported that vaccination reduces the amount of virus found in infected individuals by up to 4.5-fold, suggesting that they could

Nature; Source: *Our World in Data*

be less likely to shed that virus into the environment, where it might infect someone else.

And a study by Public Health England has found that even a single dose of either the Pfizer-BioNTech or Oxford-AstraZeneca vaccine reduced the spread of disease from infected individuals to household members by up to 50 percent. "It's likely that all the vaccines have some similar effect," says Michael Weekes, a viral immunologist at the University of Cambridge. "Overall, it's quite an optimistic picture."

But faced with incomplete data, these studies must often rely on inference to draw conclusions—assuming, for example, that lower viral load translates to reduced transmission, says Susan Little, an infectious disease specialist at the University of California, San Diego. Little is an investigator on an ambitious trial spread across more than 30 higher-education institutions in the U.S. to determine how often vaccinated people infect others. The trial will randomize students so they either receive the Moderna vaccine or delay vaccination by four months. Researchers will test participants daily for infection; their close contacts will take coronavirus tests twice a week.

Little and her colleagues are looking for high-quality data to back up important decisions to come. "As people are starting to go back to work, at a policy level, should vaccination be required for schools, places of employment, public transport?" she asks. "Do vaccinated individuals need to wear masks or social distance?" On May 13 the U.S. Centers for Disease Control and Prevention revised its guidelines on masking, saying that fully vaccinated people could go without masks in some public settings.

But Little says widespread vaccine availability in the U.S. has left the study struggling to enroll participants. And the spread of viral variants could complicate the picture still more, Kim says. If vaccines are less able to decrease the viral load in individuals infected with a variant, they might also be less able to block transmission, he cautions. "Transmission is a really hard one," he says. "And an unknown variable here is how the variants will affect this."

WHAT HAVE SCIENTISTS LEARNED ABOUT SAFETY?

The speed at which countries have rolled out COVID-19 vaccines is unparalleled—and the same can be said of the surveillance systems put in place to monitor vaccine safety.

Clinical trials of some vaccines involved more than 40,000 participants and yielded few signs of side effects beyond those often seen after vaccination, including injection-site soreness, fever and nausea. "We generally say that no vaccine is 100 percent safe," Meissner says. "But the safety of these vaccines is remarkable."

Shortly after inoculations with the Pfizer-BioNTech vaccine began, a few regions reported cases of a severe allergic reaction called anaphylaxis. But further study showed that the risk of this condition—which can be treated at the vaccination center—is not much higher for the Moderna and Pfizer-BioNTech jabs than for other vaccines, Meissner says. For Pfizer-BioNTech, the risk is about 4.7 cases per one million doses; the risk of anaphylaxis from any vaccination is estimated at 1.3 in a million.

More concerning has been the very rare occurrence of a blood-clotting syndrome in recipients of the Oxford-AstraZeneca and Johnson & Johnson vaccines. First reported in Europe and linked to vaccination with the Oxford-AstraZeneca vaccine, hallmarks of the syndrome include blood clots in unusual places—particularly in the brain and abdomen—coupled with depletion of clot-promoting cell fragments called platelets. The condition can be fatal, but regulators have repeatedly determined that the risk posed by COVID-19 is greater for many people than is the risk of developing the clotting syndrome. The European Medicines Agency has concluded that it occurs in about one in 100,000 vaccine recipients.

Researchers are still racing to determine how the vaccine could cause the syndrome. But the subsequent U.S. discovery of similar cases among recipients of the Johnson & Johnson vaccine—although at a frequency of only about 3.5 per million people—has led to speculation that the condition might be linked to the disabled adenoviruses used in the vaccines to shuttle the coronavirus spike gene into cells.

Since the syndrome was discovered, the U.K. has advised that people under the age of 40 receive a different vaccine, given their very low risk of complications from SARS-CoV-2 infection. The U.S. has resumed vaccinations with the Johnson & Johnson vaccine after pausing it in response to the reports. But in Denmark, the Oxford-AstraZeneca vaccine was discontinued in April, and those who have already received one dose have been advised to have an mRNA vaccine from Pfizer-BioNTech or Moderna as their second dose.

Meanwhile surveys have suggested that the debate over the safety of these vaccines was enough to damage public confidence in them. "What defines a safe vaccine?" Meissner says. "One out of 100,000 may seem very safe for one person; another person says, 'One in a million? What if that's me?' "

Israel's Ministry of Health is now evaluating a possible link between the Pfizer-BioNTech vaccine and reports of heart inflammation, a condition called myocarditis. So far most cases have been mild and have occurred in men aged between 16 and 19.

WHAT IMPACT HAVE THE VACCINES HAD ON THE COURSE OF THE PANDEMIC?

Several countries with high vaccination rates—including Israel and the U.K.—have seen precipitous declines in deaths and hospitalizations from COVID-19. Public Health England has calculated that the vaccines have saved 13,000 lives among those 60 years and older. The U.K. has

fully vaccinated more than one third of its population.

But these countries have conducted their vaccination campaigns while under strict social-distancing measures. Chile, in contrast, rolled back its distancing requirements early this year as it embarked on an aggressive vaccination campaign. By April its intensive-care wards were overflowing with COVID-19 patients, despite the country having one of the world's highest vaccination rates.

Once vaccines have reached a wide swath of the population, however, it might be possible to ease lockdowns and social-distancing restrictions. Israel's rates of infection, for example, have remained low after it gradually relaxed most restrictions once about half of its adult population had been vaccinated. Infections are also falling in the U.S. as the proportion of fully vaccinated adults there surpasses 40 percent.

But the Seychelles, the most vaccinated country in the world (with a population of fewer than 100,000), experienced a surge in infections—although relatively few deaths—as it reached a level of more than 60 percent adult vaccination in early May.

For now, it's unclear what has driven that outbreak and whether coronavirus variants could be to blame, Kim says. But it pays to ease restrictions slowly, he says, even once a country has achieved a high level of vaccination. "It's probably wise to remember that every time we saw the numbers going down and we were relieved and relaxed, they came back again," Kim says. "That's the cautionary tale in all of this."

And for much of the world—particularly low- and middle-income countries—limited supplies mean that vaccines will probably have little impact on the course of the pandemic this year. Madhi says that he does not expect the current roll-out in South Africa to do much to protect it from the impending third surge there: by the time all people over the age of 60 have been offered their first dose at the end of June, he expects social distancing and other measures to have already brought the country's burgeoning infection numbers down. And in India, a combination of low vaccination rates, aggressive variants and widespread social interaction are thought to have led to its tragic and overwhelming COVID-19 outbreak.

A health worker administers doses of the Oxford-AstraZeneca vaccine by the Amazon River in Brazil during a flood.

Bruno Kelly *Alamy*

Whereas some wealthy countries were able to preorder large amounts of vaccine, many low- and middle-income countries have had to make do with less. The World Health Organization's target is to vaccinate 20 percent of the population in those countries by the end of 2021. "This is not going to be the main exit strategy for them this year," says Mark Jit, an infectious disease modeler at the London School of Hygiene & Tropical Medicine. "Maybe in 2022, when the supply is less constrained." Such countries might need to rely heavily on social distancing, mask wearing and test-and-trace programs.

And even in countries with higher vaccination rates, the once glittering hope of achieving herd immunity—when enough immunity exists in the population to prevent disease spread—has faded, Kim says. "Now with widespread generation of these variants and continued uncontrolled outbreaks, that's looking less likely," he says. "And the impact of the pandemic will continue to be felt until vaccination can be accomplished not only in high-income but low- and middle-income countries." SA

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After COVID-19 Successes, Researchers Push to Develop mRNA Vaccines for Other Diseases

mRNA vaccines are now in the limelight as a key tool for tackling COVID-19, but the technology was originally developed for other diseases, such as cancer, that researchers are now hoping to treat

By Mike May

Alamy

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

WHEN THE BROAD RANGE OF VACCINES AGAINST COVID-19 WAS BEING TESTED IN CLINICAL trials, only a few experts expected the unproven technology of mRNA to be the star. Within 10 months, mRNA vaccines were both the first to be approved and the most effective. Although these are the first mRNA vaccines to be approved, the story of mRNA vaccines starts more than 30 years ago, with many bumps in the road along the way.

In 1990 physician-scientist Jon Wolff, who died last year, and his University of Wisconsin–Madison colleagues injected mRNA into mice, which caused cells in the mice to produce the encoded proteins. In many ways, that work served as the first step toward making a vaccine from mRNA, but there was a long way to go—and there still is, for many applications.

Traditional vaccines use a weak or inactive form of a microorganism to turn the immune system against the disease. After a person is given an injection of an mRNA vaccine, their cells make part or all of a protein that causes an immune response, including the production of antibodies. Although the most widely known examples are the mRNA-based vaccines from BioNTech-Pfizer and Moderna directed against the SARS-CoV-2 coronavirus that causes COVID-19, that is just one small part of this field—and those vaccines were not the first efforts that used mRNA.

Despite the many benefits of using this molecule as the basis of a vaccine, it comes with fundamental challenges: it is not very stable inside cells, and mRNA is not efficiently translated into proteins when used as a gene-delivery tool. Today mRNA can be engineered to battle many diseases, but it will not work with all of them.

THE UPSIDES OF MRNA

German biotechnology company BioNTech's chief medical officer Özlem Türeci—physician, immunologist and entrepreneur—says that "mRNA has a couple of interesting features that make it attractive for vaccines." Adaptability serves as this molecule's key feature in this application and beyond. mRNA can be engineered not only to make antigens for vaccines but also to encode antibodies, cytokines and other proteins related to the immune system. "The versatility of mRNA creates a huge design space," she explains.

The scientists at BioNTech spent years researching and developing techniques to get full command over mRNA, including optimizing its noncoding parts, designing specific sequences, developing manufacturing processes, and more. Türeci describes the results of those efforts by saying, "We have a diversified toolbox, and by mixing and matching the modules in this toolbox, we can design mRNA with the features that we need for a particular purpose." She adds that "it is a bit like writing code—by mastering a programming language [that] is rich in terms, one can give any instruction one wants." With the BioNTech toolbox, the scientists can control how much protein is produced and for how long, the route of administration of the mRNA, which cells express the protein and if the mRNA creates a precise activation or suppression of the immune system.

Once scientists know what mRNA they want to make, the process is relatively easy. For vaccines, using mRNA is much quicker than the traditional approach, in which the vaccine is grown in cells or in chicken eggs. To make mRNA, a scientist starts with a computer to lay out the desired sequence. Then, an in vitro transcription reaction is used to create a DNA template that can synthesize the desired mRNA. Thus, this process does not require cell culture or animal material, and the manufacturing process stays mostly the same regardless of the sequence of the mRNA.

ENHANCING THE APPROACH

Although the high efficacy of mRNA vaccines seems miraculous in the fight against COVID-19, that is far from the whole story. Wolff's work in the 1990s set off interest in using mRNA vaccines, but scientists ran into a fundamental problem: "RNA is highly inflammatory," says physician-scientist Drew Weissman of the Perelman School of Medicine at the University of Pennsylvania.

In 2005 Weissman and his then colleague Katalin Karikó—now at BioNTech—found a way to make RNA less inflammatory. They showed that the inclusion of modified nucleosides, part of the basic structure of RNA, resulted in a dramatically lower inflammatory response. This work explored the use of nucleosides such as 5-methylcytidine, pseudouridine and other forms. With these modifications, Weissman says, "you could increase the amount of protein that mRNA could make by 10- to 1,000-fold and make a much better vaccine." Plus, chromatographic techniques can remove contaminants, such as double-stranded mRNA, which results in an even lower inflammatory response.

A decade later Niek Sanders—the principal investigator at Ghent University's laboratory of gene therapy and scientific founder of Ziphius Vaccines—and his colleagues found a different modification for mRNA. mRNA that incorporated the N1-methylpseudouridine modification by itself or with 5-methylcytidine produced as much as 44-fold more of its intended product than mRNA with previous modifications produced, and it still resulted in a diminished immune attack on the molecules. "This is still the best modification, and it is also used in the COVID-19 mRNA vaccines of BioNTech-Pfizer and Moderna," Sanders says.

"We have a diversified toolbox, and by mixing and matching the modules in this toolbox, we can design mRNA with the features that we need for a particular purpose."
—Özlem Türeci

CONSTRUCTING A CARRIER

Chemically modified or not, just injecting mRNA alone will not work. "Naked mRNA gets destroyed and [is] not taken up by cells," says microbiologist Justin Richner of the University of Illinois College of Medicine at Chicago. Once the mRNA is injected, extracellular ribonucleases cut it up.

Various versions of lipids, such as ionizable lipid nanoparticles, can be used to safely deliver the mRNA to target cells. Türeci and her colleagues optimized a therapy with what she describes as "different liposomal formulations to make RNA fit for the respective purposes like an intramuscular or intravenous injection and targeting specific cell types." BioNTech found that for anticancer vaccines based on liposomally formulated mRNA, for instance, the antigen is expressed mainly in the dendritic cells in lymphatic compartments. These cells specialize in setting off antigen-specific immune responses.

In the future, scientists hope to have far more control over the resulting protein production. In a collaboration that included synthetic biologist Ron Weiss of the Massachusetts Institute of Technology and others, Sanders described switchable mRNA. "It's an on/off switch for mRNA," Sanders says, "and we proved that it works in mice." With this form of mRNA, the therapy can be turned on when needed, and the level of protein production can be more precisely controlled.

Each of these improvements—less inflammation, increased expression, protected delivery and controlled protein production—allows researchers to build better vaccines based on mRNA.

IMPROVING VACCINES AGAINST INFLUENZA

Among the most commonly used vaccines, the vaccine against influenza is perhaps in need of the most improvement. This vaccine is estimated to prevent tens of thousands of hospitalizations each year. Yet data from the U.S. Centers for Disease Control and Prevention on vaccines against seasonal influenza for 2009–2020 indicate an average effectiveness of about 43 percent. In this period, even the most effective vaccine, for 2010–2011, reached an efficacy of only 60 percent, and in the worst case, in 2014–2015, it reached an effectiveness of only 19 percent, protecting about one in five people.

In defense of these vaccines, they must track a moving target. "Influenza vaccines are the only mass-distributed bioproduct that changes routinely," says Philip Dormitzer, vice president and chief scientific officer of viral vaccines at Pfizer Vaccines Research and Development. "A big challenge with flu is keeping up with the changes."

With traditional methods of making a vaccine against influenza, developers must modify the virus or protein being made. That modification can require changes in manufacturing. For example, the modified virus might grow a little differently than expected, which might require changes in a vaccine's formulation. Plus, vendors usually start making vaccines against influenza six months in advance of using them, so by the time people get the vaccines, they might not provide protection against the most prominent influenza strains of the season.

With an mRNA-based approach, Dormitzer says, "swapping one gene for another with mRNA changes its properties very little in manufacturing, which is much easier than changing a viral strain." Speed also matters, and developers can quickly make mRNA vaccines. "The closer you can move the strain selection to flu season, the more accurate you will be," Dormitzer says. By being able to make mRNA vaccines faster, manufacturers can select

the influenza strains to target later than they are able to with traditional methods, which should increase the efficacy of the treatment.

The engineering behind mRNA vaccines also allows scientists to build multivalent vaccines. "We can go up in the number of antigens being expressed," Dormitzer explains, "which could increase the robustness of a flu vaccine."

Seeking approval for a new vaccine against influenza, however, is different than it has been for COVID-19, which had no treatment or vaccine. For influenza, there are a "number of vaccines out there, but their efficacy could be better," Dormitzer says. "So it's very important that a flu vaccine check all of the boxes: efficacy, reliability, supply, tolerance, and so on."

Consequently, a pharmaceutical company is likely to market an mRNA-based vaccine against influenza only when it surpasses existing ones in several ways.

"A very low-dose vaccination generated an immune response in all subjects. This demonstrated the potential of our mRNA technology for the first time."
—Thorsten Schüller

EXPLORING OTHER INFECTIONS

COVID-19 and influenza are just two of many infectious diseases that might be treated with mRNA-based vaccines. For instance, Weissman says, "We are working on about 30 different mRNA vaccines, including ones for influenza, HIV, hepatitis C, malaria, tuberculosis and many others." That alone shows how flexible mRNA can be for building vaccines.

One vaccine made from mRNA and lipid nanoparticles is very similar to another, Weissman notes. "The important thing is finding the right antigen," he adds. "We spend a lot of time and work with lots of experiments to find the best antigen to make a vaccine work the best."

Finding a good antigen to target is easier with some infections than with others. With HIV, Weissman says, "the envelope is the important antigen, but it mutates rapidly and it's covered in sugar, and you need to address those issues to make an antigen that produces the right response." Changes in the design of the mRNA might also be required.

Weissman and virus expert Harvey Friedman of the University of Pennsylvania found targetable antigens for genital herpes. Using these antigens, the scientists developed a vaccine from nucleoside-modified mRNA and lipid nanoparticles. Tests in mice and guinea pigs showed that this vaccine prevented infection with the virus that causes genital herpes. "This vaccine is moving into clinical trials," Weissman says.

The use of mRNA for vaccines also holds hope for previously intractable, but highly prevalent, infections with pathogens such as dengue virus. Dengue virus, which is carried by mosquitoes, endangers nearly half of the world's population and infects as many as 400 million people a year. Because there is no treatment for this infection, Richner is working on a vaccine.

"Dengue is somewhat complicated," Richner says. It consists of four different viruses that cause a similar disease. "We want to target all four," he notes. Targeting all four dengue viruses is necessary, as a subsequent infection with a different dengue virus tends to be more severe as result of antibody-mediated enhancement.

Richner and his colleagues started with dengue virus stereotype 1. Like Weissman, Richner's team used a nucleoside-modified mRNA in lipid nanoparticles. Neutralizing antibodies elicited by the vaccine were sufficient to protect mice against a lethal challenge. Now Richner's team is working on expanding this vaccine to serotypes 2, 3 and 4, and the differences in the dengue viruses require some adjustments in targeting each one. "We'll need to optimize the vaccine for each virus," he says. The goal is to provide protection against all four dengue viruses with one vaccine.

At CureVac, data from a phase 1 clinical trial of the company's mRNA-based vaccine against rabies look promising. "A very low-dose vaccination generated an immune response in all subjects," says Thorsten Schüller, CureVac's vice president of communications. "This demonstrated the potential of our mRNA technology for the first time."

CREATING VACCINES AGAINST CANCER

Before COVID-19 hit, Türeci and her colleagues at BioNTech were working on mRNA-based vaccines against cancer. "You want to confront a patient's immune system with a wanted poster of the enemy and train the immune system's effectors to recognize the enemy and teach the immune system that this is dangerous."

Türeci says that mRNA can be used to deliver two types of cancer antigens. The first approach is to present to the immune system a person's own antigens that are usually shut down in healthy cells—antigens encoded by embryonic genes would be an example of this—but are expressed by the cancer. Here an anticancer vaccine would trigger an attack on cells carrying those antigens. "For each cancer indication, we use computer algo-

rithms and machine learning to identify the antigens that cover as many patients as possible." For melanoma, as an example, four antigens cover more than 90 percent of the patients. BioNTech made a multivalent RNA-based vaccine that targets all four antigens and is in clinical trials.

Alternatively, an mRNA-based vaccine can target a cancer's mutations. The profile of mutations, however, is unique to each patient, and that requires a personalized approach. "This is the perfect playground for mRNA," Türeci says. "We start from a patient profile, generate a multivalent, multimutation vaccine in four weeks for this patient and treat them with it." This method, which is in several clinical trials run by BioNTech and Genentech/Roche, uses a approach similar to that used for making the BioNTech-Pfizer vaccine against COVID-19. Türeci describes the strategy as analyzing "genetic information to tailor a vaccine and manufacture it fast." She adds, "We had already done that hundreds of times for our cancer patients," which explains some of the speed behind the development of their vaccine against COVID-19 and why she and her colleagues feel prepared to adapt to viral variants, if necessary.

For solid tumors, an attack by the immune system is not enough. The tumor's microenvironment fights off the immune response in various ways, including suppressing the actions of T cells. For melanoma, says biophysicist Leaf Huang of the University of North Carolina at Chapel Hill, "the tumor microenvironment is the real barrier for these vaccine treatments." A vaccine must be combined with another treatment that modifies that microenvironment, allowing the vaccine-triggered T cells to enter the tumor tissue. Huang and his colleagues combined a vaccine with the chemotherapy sunitinib and found that this combination helped immune cells reach the tumor and thereby increased the efficacy of the vaccine. Cytokines such as IL-12 are also good candidates for breaking the immunosuppressive tumor microenvironment, according to Sanders, whose team successfully combined IL-12 gene therapy with a gene-based anticancer vaccine.

Nevertheless, Huang says, "the development of agents that can be used safely and effectively to modify the tumor microenvironment still has a long way to go."

EXPANDING INNOVATION

In many ways, mRNA vaccines are just getting started. "We do not have a platform for every disease, but the great advantage of mRNA vaccines is that we can test novel hypotheses in rapid succession," Richner says. "For new vaccines, we need to find what makes a good immune response, and that requires basic science."

This field will drive more basic science for years. Plenty of engineering will be involved as well. At BioNTech, Türeci calls the company's vaccine scientists "immune engineers," and she envisions many advances ahead. As she thinks of the future possibilities for mRNA vaccines, she says, "it's about the nature of innovation—not one invention but finding out what is possible in many things and bringing them together." SA

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POLICY & ETHICS

We're Overlooking a Major Culprit in the Opioid Crisis

Pharmaceutical companies and drug dealers have been part of the problem—but so have policy makers

Matt Anderson *Getty Images*

Journalists have largely presented the overdose crisis as a story of three interconnected and perhaps inevitable waves. First, drug companies, led by Purdue Pharma, maker of the notorious OxyContin, convinced gullible doctors to prescribe unneeded opioids. This led to hundreds of thousands of new addictions in the 1990s and 2000s. Observational research suggested that opioid prescribing was linked with increased disability and decreased productivity.

And overdose deaths began to rise.

The second wave in this narrative begins around 2011, when states cracked down on "pain clinics" that were really pill mills, offering doses for dollars. Prescriptions became scarce, prices rose and people who were addicted began to turn to heroin, which was cheaper and now had a big enough pool of customers to attract cartels to places that they'd never served before. Again, overdose deaths increased.

Finally, the third wave was initiated by dealers about four years later. Seeing a chance to make even more money, they began to cut heroin with illicitly manufactured fentanyl and various other synthetic opioids, which are both cheaper to make and more potent. Once again, addiction worsened. Nearly 100,000 people are thought to have died from overdose in 2020, the deadliest toll from overdose in American history.

This is the story being told in ongoing litigation

against Purdue and other manufacturers and distributors of opioids. It's being told now in West Virginia in a case against the three major distributors to pharmacies—a case seen as a landmark for thousands of similar cases.

But while the media has focused on the harm done by Big Pharma, it has largely ignored the greater damage done by policies intended to solve the problem.

Advocates led mainly by a group called Physicians for Responsible Opioid Prescribing made the case to policy makers and politicians that since overprescribing caused the epidemic, reducing medical use would solve the problem. And they did succeed in significantly shrinking the medical supply: since 2011, opioid prescribing has been cut by more than 60 percent.

Unfortunately, however, as medical use declined, the total number of overdose deaths more than doubled between 2011 and 2020. Indeed, even before the pandemic, more overdose deaths had occurred since prescribing began to fall than took place while medical opioid use was soaring.

The fact that cutting the medical supply could potentially make matters worse didn't seem to factor in to the calculations of those who supported this approach. But this outcome was, in fact, completely predictable—so much so that the phenomenon has an academic name, "the iron law of prohibition."

Coined by activist Richard Cowan in 1986, the phrase refers to the effects of reducing drug supplies while not acting significantly to manage demand. Almost always, it results in the rise of a more harmful drug because of a simple physical fact: hiding smaller things is easier than hiding bigger ones. So, because illegal drugs need to be concealed, prohibition favors more potent and therefore more potentially deadly substances.

This was seen even during alcohol prohibition, when hard liquor was preferred for sale over lower-alcohol wine and beer. Whisky is roughly eight times more potent than beer—thus, it's much easier to stash. Hence, we refer to alcohol smugglers as bootleggers, because they could hide flasks in their boots—not, say, "barrel hiders."

During today's overdose crisis, the iron law meant that when people with addiction lost access to pharmaceuticals like oxycodone (the active drug in OxyContin), they created a massive demand for street opioids. Historically, the most common of these has been heroin, but aided by the Internet, dealers soon found a cheaper and more potent substitute: fentanyl and similar synthetics, which can be hundreds to thousands of times stronger.

It's not clear what the thinking was here: Did policy makers believe that simply taking away drugs cures addiction? Or pain? Regardless, drug dealers were far more nimble than the government, often trolling for customers outside the offices of shuttered pill mills.

There's also another reason that this supply-side policy was predictably dangerous.

That is, legitimate pharmaceuticals are required to be of a standard dosage and purity, which means that people know how much they are taking and whether it's more or less than usual. Street drugs, in contrast, are unregulated. It's difficult to be sure what's in that mystery pill or powder, let alone what the appropriate dose should be.

Though advocates of cutting the medical supply argued that prescription opioids are just "heroin pills," and should be seen as similarly risky, this misses a critical distinction. If pharmaceutical and street versions of drugs are in fact equally safe, there'd be no need for regulators like the FDA.

Though advocates of cutting the medical supply argued that prescription opioids are just "heroin pills" and should be seen as similarly risky, this misses a critical distinction. If pharmaceutical and street versions of drugs are in fact equally safe, there would be no need for regulators like the FDA. Sure, people can misuse both, but with pharmaceuticals, at least they have the option of dosing more safely. This fact makes using street drugs more deadly.

Moreover, it's not like policy makers couldn't have acted on the demand side. We have two medications—buprenorphine (brand name: Suboxone) and methadone—that are proven to

cut the overdose death rate by 50 percent or more. We could have immediately made them available to patients with addiction when shutting down rogue doctors.

And this would have been a far easier task than trying to track down and treat people who use illegal drugs after their suppliers were taken down. Unlike street dealers, doctors must have a list of the real names of the patients to whom they prescribe: pharmacies require a government ID such as a driver's license to dispense controlled substances.

If the goal of reducing prescribing were actually to help addicted people and improve pain care, these patients could have been contacted and given immediate access to appropriate treatment for their medical conditions when they lost their doctors. This would have left far fewer customers for dealers.

Instead, however, supply was simply cut, and, in some cases, thousands of people were left to suffer withdrawal at the same time. As the crackdown progressed, even doctors who see their patients as benefiting from opioids began either to reduce doses or to stop prescribing entirely for fear of being targeted by police and medical boards. Now half of all general practitioners will not even accept new patients who have lost their doctors and want to continue opioid treatment.

Health departments can see the problem coming when pain clinics shut down. These days some even issue alerts about a likely rise in overdose calls. But if the goal here is to save lives, why are these patients left at risk without even being offered help first? (The only published example I've found of law enforcement trying to aid patients in this situation was during a huge 2019 raid; why is this a rarity rather than the rule?).

Further, none of this addresses the increased disability and suicidal thoughts that can occur when pain patients are deprived of the only treatment that they have found to bring relief. Though opioids were certainly overused, some intractable pain patients do benefit, and only lip service has been given to helping them. The result is that hundreds of thousands of people have simply had their opioid medications reduced or eliminated, regardless of whether this improved or destroyed their lives.

And research suggests that these cuts often haven't helped people with pain. One study of millions of medical records, which compared the timing of state opioid regulations and reductions and could therefore suggest causality, found that opioid reductions actually led directly to increased disability, decreased productivity, rising medical costs and more pain. Another study found that among veterans who had their opioids stopped involuntarily, 9 percent became suicidal and 2 percent actually tried to take their own lives. Even worse, other research shows that rather than minimizing overdose risk, cutting access to medical opioids nearly triples the odds of overdose death among people in pain.

Journalists continue to echo the three-wave story that places the blame overwhelmingly on pharma. But the second two phases didn't just happen: they were driven by policy choices.

And few have called for accountability for those who initiated the medical supply crackdown that drove the rise of fentanyl.

So, where is the reckoning for policy makers, from the DEA to the CDC to Congress and state legislatures, who closed pill mills and wrote laws, guidelines and regulations to decrease prescribing, while making no significant effort to immediately treat any of the abandoned patients, whether they were addicted or in pain, or both?

Why are we still spending hundreds of millions of dollars on policing and cutting the medical supply, while more than 80 percent of people with opioid use disorder still don't have access to effective treatment and while the vast majority of overdose deaths are now caused by street fentanyl and its chemical cousins, not prescriptions? Why do we ignore the fact that most opioid addictions start when people take drugs that are not prescribed to them?

Of course, there are potential negative effects from many kinds of policies, and lawsuits really aren't the best way to hold policy makers accountable. Moreover, unlike in Purdue Pharma's case, many of these efforts were made in good faith.

But if we actually want to use the money obtained by suing drugmakers effectively, we can't ignore the fact that the supply-side "cure" that we've enacted so far has actually worsened the disease. It's understandable to want to punish drugmakers for the genuine harm they have caused. To do better, however, we need to base policy on evidence, not emotion.

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POLICY & ETHICS

Biomedical Research Falls Short at Factoring in Sex and Gender

Despite policies that endorse more inclusiveness, incentives work against including female subjects in experiments

Picture a person having a heart attack—what do you see? Mostly likely a man, looking sweaty and short of breath, clutching his arm or chest in pain. This canonical image has been so deeply impressed into our minds that it may be hard to believe heart attacks could look like anything else. But when women have heart attacks, their symptoms can be quite different, presenting as deep fatigue, nausea and vomiting, and more widespread bodily discomfort instead of localized pain.

Discrepancies like this—between what we expect a medical condition to look like and the various forms it might take in real life—can have devastating consequences. Most often men's symptom profiles are considered the "textbook

Research on heart attacks has historically focused on male subjects only, but women's symptoms are different.

Lara Belova *Getty Images*

cases," and so when women present with different symptoms, they may be misdiagnosed, resulting in delays or possible deprival of life-saving interventions. To exacerbate things further, women are more likely to report later to the hospital (defined as waiting 12 hours or longer after symptom onset) than men, a consequence in large part of the confusion over symptomology.

The failure to consider the influence of sex and gender on health physiology goes beyond the clinic. In laboratories around the world, most scientists have historically chosen to study only male rats and mice, under the faulty assumption that female animals' fluctuating hormones would make their data messy and hard to interpret. Like humans, female rodents undergo reproductive cycles characterized by phases of high and low circulating estrogen, which has the potential to influence experimental outcomes.

What most researchers fail to acknowledge, however, is that males also display significant daily fluctuations in hormone levels (primarily testosterone), which may also influence experimental outcomes. Interestingly, recent analyses of thousands of scientific publications found that data collected from male and female rodents are pretty much equally "messy," and if anything, males displayed more variability overall than females! Thus, this type of overall noise in scientific results is normal.

What have we been missing by excluding female animals from preclinical research? In our field of neuroscience alone, we see evidence for sex differences in a wide variety of neural processes, including spatial navigation, learning strategies and pain transmission, demonstrating that evolution has equipped the mammalian nervous system with not one but multiple ways to experience and adapt to the world around us. But despite these exciting findings, investigations into the biological mechanisms that underlie fundamental phenomena such as memory or sensory processing have by and large been conducted only in males. Even when studying diseases that affect more women than men, like Alzheimer's disease, major depressive disorder or stroke, scientists more often than not chose to work exclusively with males.

In laboratories around the world, most scientists have historically chosen to study only male rats and mice, under the faulty assumption that female animals' fluctuating hormones would make their data messy and hard to interpret.

In recent years the government agencies that fund biomedical research, such as the National Institutes of Health in the U.S., have begun to recognize that the neglect of females as research subjects may lead to serious public health problems as basic science findings make their way into the clinical pipeline for treatment. In addition to misdiagnoses, women are more likely to experience negative side effects from drug treatment, possibly a consequence of those drugs not being tested in female rodents during the early stages of drug discovery. To address these issues, the NIH implemented a policy in 2015 mandating consideration of "sex as a biological variable" (SABV). This initiative requires scientists applying for funding to incorporate both male and female animals into their experimental designs unless a research topic, such as pregnancy, is by definition sex-specific.

More important, SABV guidelines do not require scientists to specifically assess sex differences in their studies. Yet many scientists initially protested (and continue to do so) that the new policy would require them to essentially double the number of animals they used, thereby preventing their grant dollars from stretching as far. Others claimed that they would in fact have to quadruple their animal numbers to account for every phase of the female reproductive cycle. The idea that hormones are a critical consideration for research in female subjects, but not male subjects, is rooted in long-standing sexist stereotypes that contradict actual scientific evidence. Males, of course, have hormones, too, which can rise or fall depending on their social hierarchy status in their cage, the type of food they are fed, and the time of day. But as we note earlier, fluctuating hormones in animals of either sex do not create the problematic, "messy" data sets that many scientists have assumed.

Requiring the use of male and female animals in biomedical research is an important first step in disabusing scientists (and society) of the flawed notion that males are a standard from which females might deviate. As we can see in human medicine, treating men's cases as the default measuring stick can have dire consequences; rather treating all research subjects as equally valuable in our quest for knowledge is critical to rectifying sex- and gender-based health disparities.

Unfortunately, there is yet another force working against the rapid adoption of SABV practices: the culture of academic publishing. The expression “publish or perish” probably rings true for most researchers. But the real currency in academic science is not just any publication but a paper in a high-profile journal like *Science* or *Nature*. These journals are known for being extremely selective in what they choose to publish, and having a *Science* or *Nature* paper is often an unspoken requirement for faculty hiring and promotion at prestigious universities. Yet these journals have historically valued preclinical research that takes a deeper dive into its topic within a single sex (usually males) rather than research that takes the time to ask questions in both males and females. We therefore end up with an incentive structure that pits personal prestige and career advancement against more rigorous, equitable investigations into biological processes and mechanisms of disease.

In 2016 the journal *Research Integrity and Peer Review* published guidelines for Sex and Gender Equity in Research (SAGER), which provide clear steps for scientists and editors to increase equity, accuracy and transparency in both the conduct and reporting of research in subjects of both sexes. These guidelines clearly state that experiments should be designed to reveal sex or gender differences and that single-sex studies require justification for the exclusion of either sex. Sadly, few (if any) journals have incorporated these guidelines into their publishing policies.

The world of biomedical science is long overdue for a realignment of its reward systems with public health goals. Human bodies and brains are complicated, and our job as basic scientists is to lay the foundational knowledge that will ultimately inform personalized medicine. This should mean embracing the noise—seeing variability in experimental outcomes as an opportunity to understand the scope of what is possible, not an inconvenience to be swept under the rug in the futile pursuit of a single and rapid “right” answer.

But as long as high-profile journals continue to put their seal of approval on work that examines only males, scientists will continue to deprioritize research in female subjects or simply not do it at all. Journal editors, peer reviewers, tenure committees and others in gatekeeping positions have the power to shape what prestigious science looks like. It's time to step up and shift scientific culture to value rigorous research that includes both sexes.

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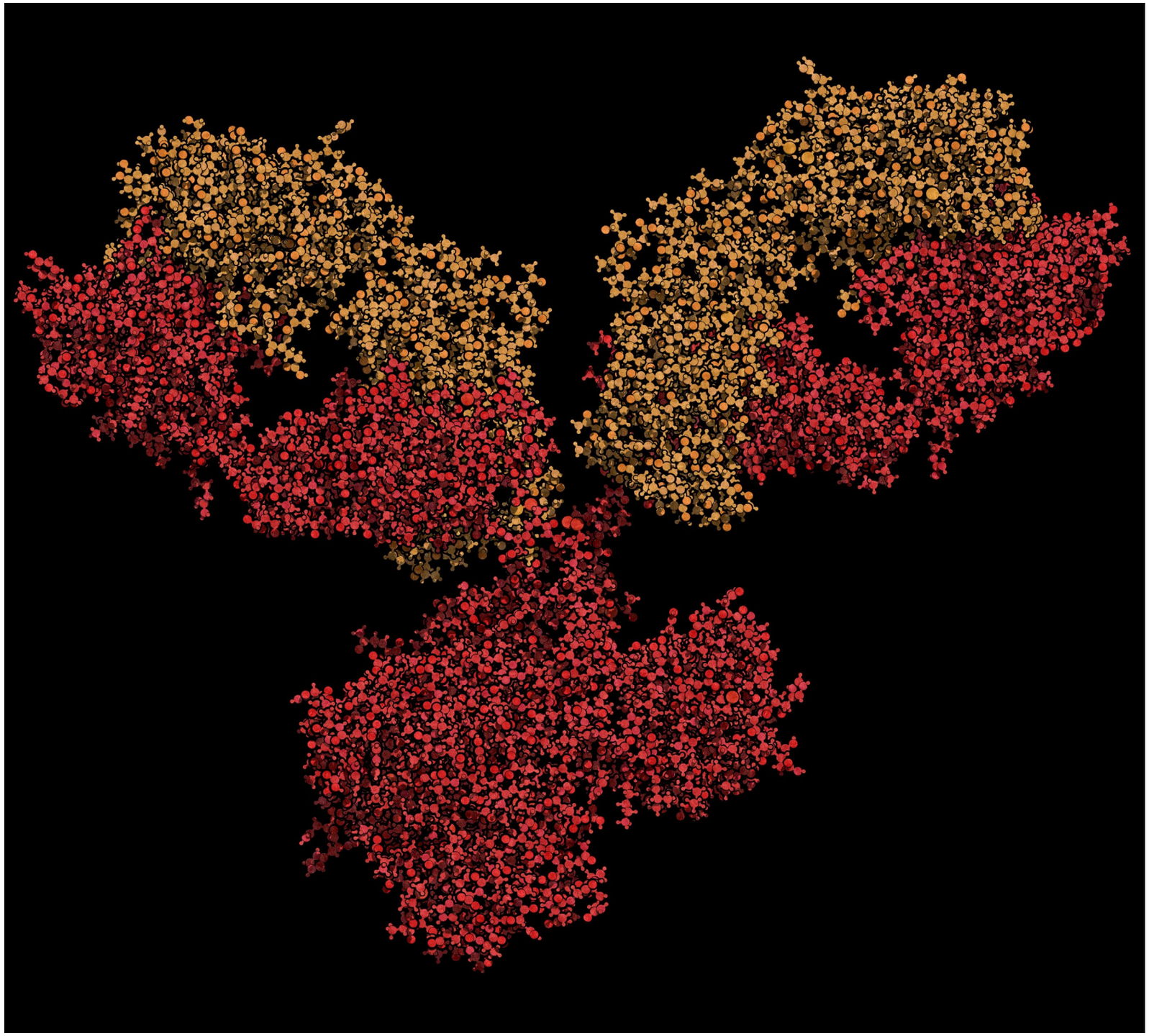
PUBLIC HEALTH

Why Monoclonal Antibody COVID Therapies Have Not Lived Up to Expectations

The drugs used to treat Donald Trump have not been widely administered to other patients, but they still have a role to play



Getty Images

Over the past year the successful development of highly effective vaccines to prevent SARS-CoV-2 infection has moved forward at a rapid pace—but the use of treatments for patients sickened by the virus has lagged. A number of barriers have stood in the way of using the drugs known as monoclonal antibodies, including logistical challenges and the emergence of new viral variants that are resistant to some of these antibodies. Although they are not a cure for COVID, monoclonals can serve as an effective therapeutic option that can prevent a patient with mild or moderate disease from becoming sicker and ending up in the hospital.

Monoclonal antibodies are laboratory-made molecules that in this case mimic the immune system response to SARS-CoV-2, targeting a specific portion of the protruding "spike" proteins on the surface of the virus, preventing it from binding to cells or tagging it for destruction. Researchers first isolate antibody-producing B cells from patients who have recovered from COVID. They go on to find the most potent of these antibodies and then produce them in mice engineered with components of the human immune system.

The use of monoclonal antibodies for the treatment of COVID gained national and international attention in October 2020, when President Donald Trump received an antibody cocktail made by Regeneron after he was diagnosed with the illness. Shortly thereafter, two monoclonal compounds received emergency-use authorization (EUA) by the U.S. FDA and were expected to be a key part of the response to the pandemic.

But a number of factors have limited their use. There has been a rise in more contagious SARS-CoV-2 variants, some of which exhibit decreased susceptibility to the monoclonal antibodies. Difficulties have also arisen in administering these compounds to outpatients with mild and moderate disease in overwhelmed hospitals. Nevertheless, the use of these drugs can still slow disease in some patients who are at risk of worsening, and they may also be useful in prevention.

Today there are several monoclonal antibodies that have been studied and for which the FDA has given EUA. This designation is not a formal approval, but it lets drugs be used during public health crises. Drugs with EUAs initially included bamlanivimab (also known as LY-CoV555 and LY3819253), etesevimab (LY-CoV016 and LY3832479), casirivimab (previously REGN-10933) and imdevimab (previously REGN10987). In November the FDA granted an EUA for both bamlanivimab and, separately, the combination of casirivimab/imdevimab for use in outpatients with mild to moderate COVID who are at high risk of progression to severe illness.

For monoclonals to be more widely distributed, the possibility of administering them subcutaneously or intramuscularly rather than intravenously should be explored. We should also move their administration from the clinic into pharmacies and testing sites where it can be more easily and readily done.

These approvals were based on an interim analysis of two midstage (phase II) clinical studies among outpatients with mild to moderate COVID in which these compounds appeared to accelerate the decline in viral load in a patient. But because of an increase in the number of SARS-CoV-2 variants resistant to bamlanivimab (from approximately 5 percent in mid-January to 20 percent in mid-March 2021), the FDA revoked the EUA for bamlanivimab on April 16, 2021, and it is no longer available for use as a sole treatment for patients. Nevertheless, two products that combine monoclonals (bamlanivimab plus etesevimab or casirivimab plus imdevimab) are still available through an EUA for the treatment of mild to moderate COVID in nonhospitalized patients at high risk of progressing to severe disease or hospitalization. None of these drugs have been shown to be of benefit in sicker hospitalized patients.

Currently the NIH COVID treatment guidelines recommend that one of the two cocktails be administered for the treatment of outpatients diagnosed with mild to moderate COVID infection who are at high risk of progression to severe disease. The treatment criteria include having a body mass index of 35 or more, being 65 or older, having diabetes, chronic kidney disease or an immunosuppressive disease, or taking an immunosuppressive drug. Some people younger than 65 are also eligible if they meet specific requirements. Data on the use of these drugs for patients younger than 18 years old are limited.

When prescribing these therapies, it is important that treatment be started as soon as possible after the diagnosis and within 10 days of onset of symptoms. The Infectious Disease Society of America guidelines note that the data are stronger for bamlanivimab/etesevimab than for casirivimab/imdevimab. But they also recommend

that prescribers take into account which variants are circulating in the community and whether or not they are susceptible to monoclonal treatments.

The rollout for monoclonals came only slightly before the introduction of highly effective vaccines. With the vaccines' arrival, monoclonals have not been as widely used as originally contemplated and are being reserved for people who cannot be vaccinated, those who do not respond to the vaccine or people who need immediate prophylaxis after a significant exposure.

After Trump was treated with monoclonals and after the FDA issued its EUA, the federal government purchased more than 500,000 doses of both bamlamivimab and casirivimav/imdevimab, expecting high demand for these drugs. Not only was the demand from patients weaker than projected but hospitals and clinics struggled to get these treatments to patients.

There are several explanations as to why. Patients sometimes delay seeking care until more than 10 days after the onset of symptoms. Test results may lag. Logistical issues emerge in administering an infusion or injection at a site where a patient with COVID can be safely seen. Probably the largest barrier over the December-to-January period was that hospitals were overwhelmed with sick patients and simply lacked the staff to administer these drugs to patients who were "not sick enough."

So, do I still think these are useful drugs? Absolutely. We are currently recording around 60,000 new infections a day in the U.S., and many are occurring among persons who would benefit from monoclonal antibody therapy to prevent progression of COVID to severe disease and hospitalization. The word about monoclonals still needs to get out. Regeneron, in fact, aired an advertisement during the 2021 Academy Awards, hoping to educate patients about the value of these compounds.

For monoclonals to be more widely distributed, the possibility of administering them subcutaneously or intramuscularly rather than intravenously should be explored. We should also move their administration from the clinic into pharmacies and testing sites where it can be more easily and readily done.

As long as we continue to have cases of COVID, vaccination should not be the only strategy we implement for control. While progress has been made vaccinating high-risk populations in the U.S., we still need to increase access to effective therapies that can prevent disease progression, hospitalization and death among those who get infected with SARS-CoV-2.

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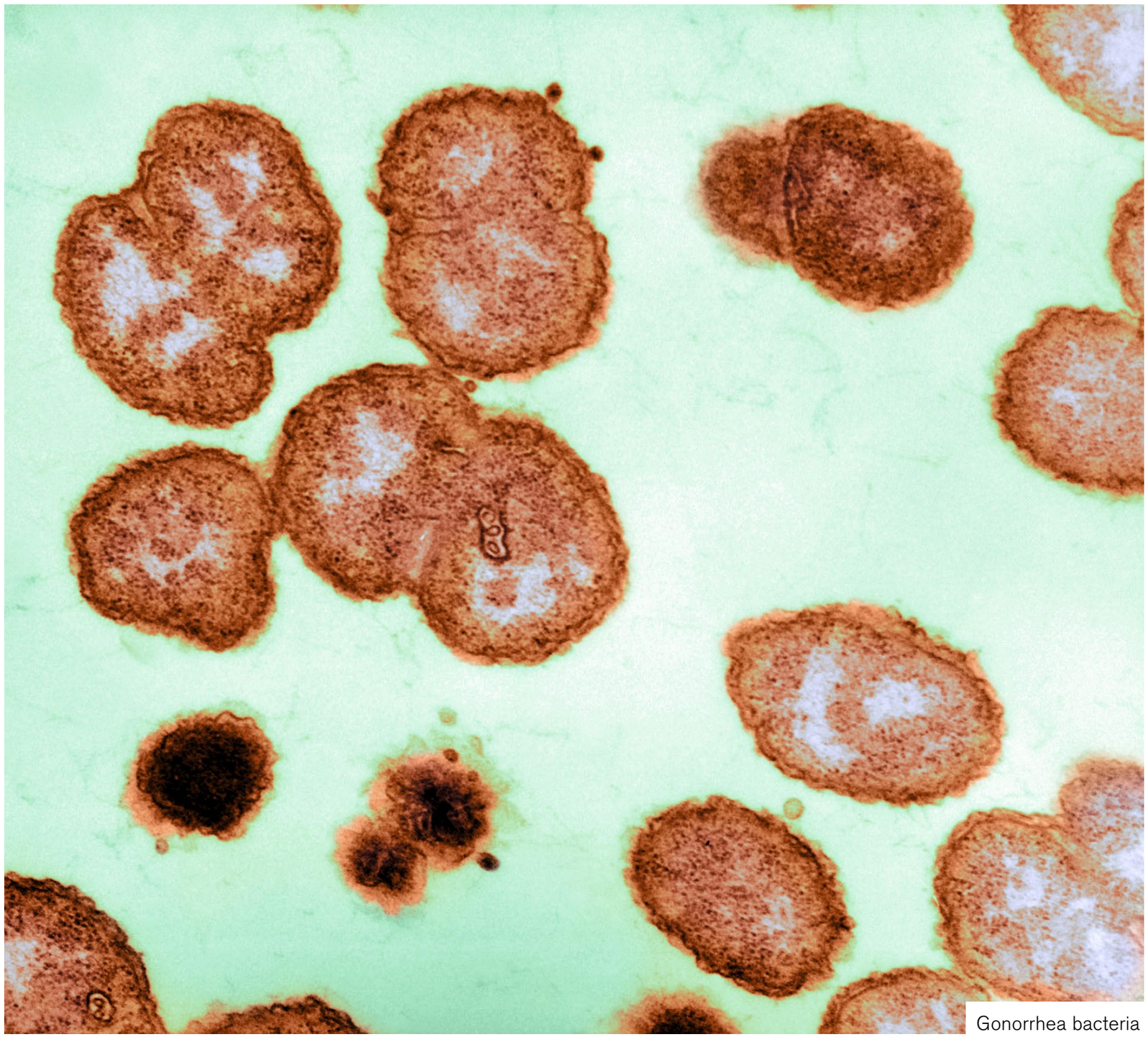
PUBLIC HEALTH

As the Pandemic Wanes, Sexually Transmitted Infections Are Likely to Rise

We created new vaccines. Now how about creating better protection against STIs?

If you were paying attention to social media recently, you might have come across a viral ad for EXTRA gum depicting scenes of postpandemic life: people slowly peeking out from behind closed doors, shutting their laptops before bursting maskless out of their toilet paper–filled dens into the street. The actors, all unwashed and unkempt, run gleefully to the nearest park where each proceeds to pounce on the first stranger they encounter and initiate a passionate make-out session, set to Celine Dion's power ballad "It's All Coming Back to Me Now."

It's been more than 100 years since the "Spanish" flu pandemic stifled our sex lives to the extent that we've experienced during COVID-19. As a



Gonorrhea bacteria

Alamy

sexual health physician and researcher, I can attest to seeing empty waiting rooms for months as people kept their social and sexual distance, their desire squelched by fear of contagion. Certainly there were some for whom pandemic-induced abstinence was short-lived, and I was gratified to see public health agencies in New York and Canada cheerfully providing guidance on the matter: encouraging masked sex or even use of glory holes in barriers such as bathroom doors to facilitate anonymous oral sex.

For the most part though, our sexual appetites languished alongside our psyches as we exhausted our energy just trying to survive. And it wasn't just Americans: studies from the U.K., China, Israel and Australia found that 40 to 60 percent of people reduced their number of sexual partners or the frequency of sex during the pandemic. As a consequence of our collective abstinence (plus a national shortage of testing kits), rates of sexually transmitted infections (STIs) in the U.S. plummeted in the second quarter of 2020, after previously reaching record highs in 2019.

Now that vaccines have arrived in the U.S. en masse, there's little holding us back from having sex again. Celine Dion's ballad would imply that our muscle memory around sex will be like that of riding a bicycle: even if we haven't done it for a while, we still haven't forgotten how. What isn't clear is whether we'll still have the drive. For nearly two decades prior to the pandemic, American sexuality had been on a downward slope, even among the most sexually active age demographic. In a study of more than 9,000 adults based on surveys from 2000 to 2018, a third of young men aged 18 to 24 reported no sexual activity in 2018; activity also declined over the study period for both men and women aged 25 to 34.

For those of us who do resume having sex, it's logical to think that a year of living with COVID, donning masks, getting tested and negotiating safe socializing would translate to discussing safer sex. Not so, says Lisa Wade of Tulane University, who has interviewed more than 120 college students about sexual behavior during the pandemic. Despite a diversity of race, sexual orientation and prior sexual experience among her study participants, when asked whether living through COVID has changed the way they think about sex and STIs, their responses are "strikingly consistent": a wrinkled nose, a look of confusion and a resounding "no."

Wade's students are testing two to three times per week for COVID and have no qualms about asking each other about their test results. Yet asking about testing for STIs does not come as naturally. STIs are still accompanied by a stigma that shrouds these discussions in judgment along the lines of, "Why would you need to test?" and "What have you been up to?" Even those who felt comfortable asking others to wear a mask can find it awkward to ask a partner to use condoms or are met with resistance when such requests are made.

Our resistance to condoms and barriers cuts across gender, age and sexual orientation. HIV researchers have long understood the concept of "condom fatigue" among men who have sex with men, a weariness experienced after years being told to use condoms by HIV-prevention campaigns. As Benjamin Klassen of Simon Fraser University found in 2019, condoms among gay men now hold similar status as public transportation: something you'd love everyone else to use without having to use it yourself.

Condoms are losing popularity with the Generation Z set as well, even though teens are the age group most likely to use condoms. According to the CDC's Youth Risk Behavior Survey, condom use by high school students during their most recent sexual encounter declined from 62 percent in 2007 to 54 percent in 2019. The outlook is even worse for dental dams, squares of latex placed over the vulva for oral sex. Juliet Richters of University of New South Wales found less than 10 percent of Australian women who had sex with women had ever used a dental dam, and only 2 percent used them consistently.

In our current era of technological innovation, it seems like we should have something better than barriers—perhaps a smartphone app or an STI-blasting laser. Yet condoms remain the only multipurpose prevention device that provides both contraception and protection against STIs/HIV. But hopefully that's set to change. Groups such as the global Initiative for Multipurpose Prevention Technologies (IMPT) are working to advance the development of at least 20 products: pills, rings, diaphragms, gels, injectables and implants, with each product providing protection against at least two conditions: unplanned pregnancy, STIs or HIV.

What about building a better condom? The Gates Foundation tried to give it a go, offering

$100,000 seed grants to companies in 2013 to develop a next-generation condom that "preserves or enhances pleasure" in order to "improve uptake and regular use." By 2019 three of the 11 initial awardees had received an additional $1 million to advance to the clinical trial stage. Whether these products survived the pandemic and will make it to market remains to be seen. At least for the moment, traditional condom sales are surging but are unlikely to endure long term as we fall back into our old usage patterns.

Then there's always hope of an STI vaccine. While there are none immediately forthcoming, new clinical trials are ongoing for vaccines against herpes and gonorrhea. And as Operation Warp Speed has shown, pharmaceutical companies can create effective vaccines quickly with enough political will and financial support.

But whether the future of prevention is a better condom, a new device or an STI vaccine is unimportant. What's crucial is having prevention products that people will actually use. If predictions of a Roaring Twenties redux or a post-COVID Summer of Love hold true, then a rise in STIs and HIV are sure to follow. It will take more than our old barrier methods to meet the current needs of our sexually diverse population. We must invest in development of new prevention products now or risk being caught with our pants down later.

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LETTERS TO THE EDITOR:
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