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Health & Medicine

August–September 2022

Plus:

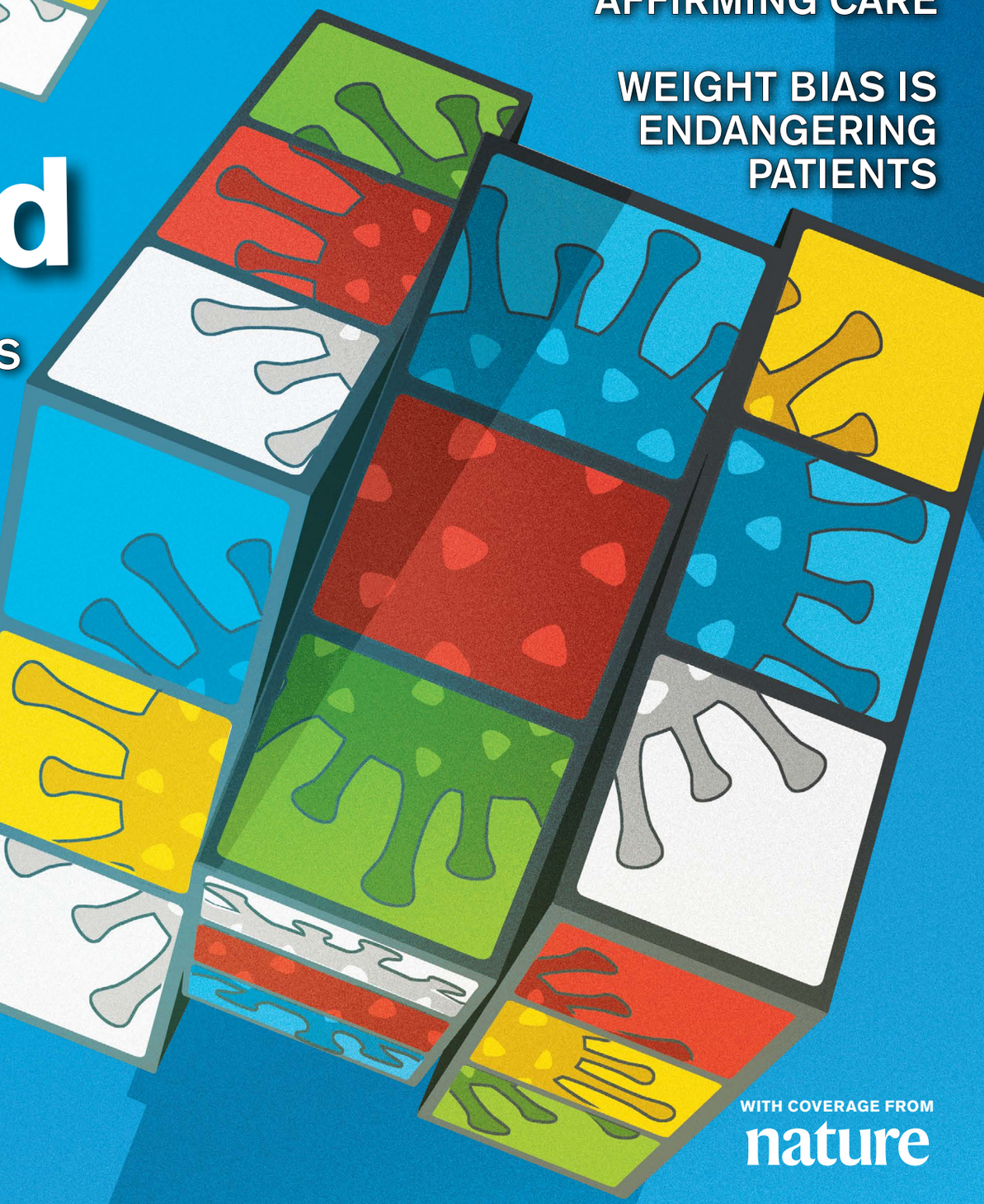
WHAT WE KNOW ABOUT MONKEYPOX

THE SCIENCE OF GENDER-AFFIRMING CARE

WEIGHT BIAS IS ENDANGERING PATIENTS

One Step Ahead

CUTTING-EDGE RESEARCH INTO HOW NEW VARIANTS OF COVID-19 ORIGINATE MAY HELP SCIENTISTS ANTICIPATE THE NEXT BIG STRAIN



WITH COVERAGE FROM nature

Liz Tormes

Solutions from Science

Another month, another variant. As of July, the version of SARS-CoV-2 called BA.5 is officially the dominant strain in the U.S., making up 54 percent of all new cases. This is unlikely to be the last variant, and each new strain, this one in particular, is highly contagious and has its own set of mutations that help it evade the immune system and existing antibodies from previous infections or vaccinations. Despite a constantly changing landscape, one thing that has remained steady since the beginning of this long pandemic is that science is ever vigilant. Researchers are studying past, present and long cases of COVID with unrelenting diligence, in hopes of perhaps predicting, if not preventing, the spread of the disease, as Ewen Callaway writes in this issue (see "Chronic Covid: The Evolving Story").

Meanwhile new kinds of vaccines in development could revolutionize how we inoculate against the virus (see "Nose Spray Vaccines Could Quash COVID Virus Variants"), and engineers are at work implementing new ways to prevent indoor transmission (see "We Need to Improve Indoor Air Quality: Here's How and Why"). Whether COVID sticks around for two more months or two more years, any solution we devise will be grounded, informed and inspired by science. And that, for me, is a cure for some uncertainty in the world.

Andrea Gawrylewski
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Health & Medicine

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Chris Gash

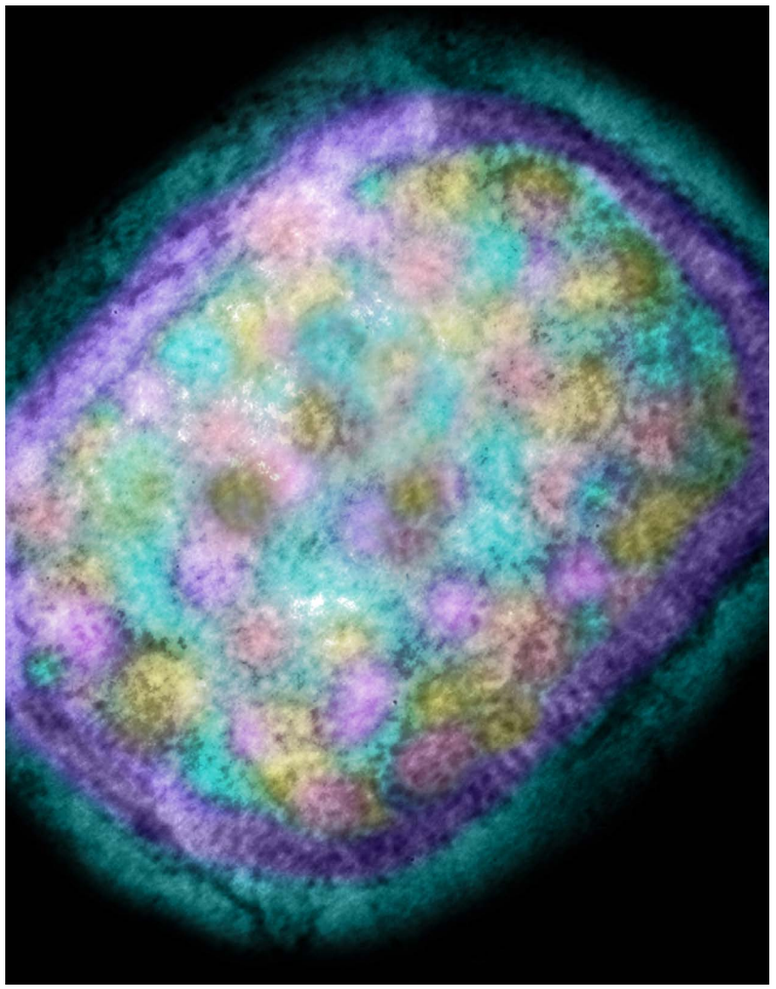
On the Cover

Cutting-edge research into how new variants of COVID-19 originate may help scientists anticipate the next big strain

WHAT'S INSIDE

August–September 2022
Volume 4 • Number 4

NEWS



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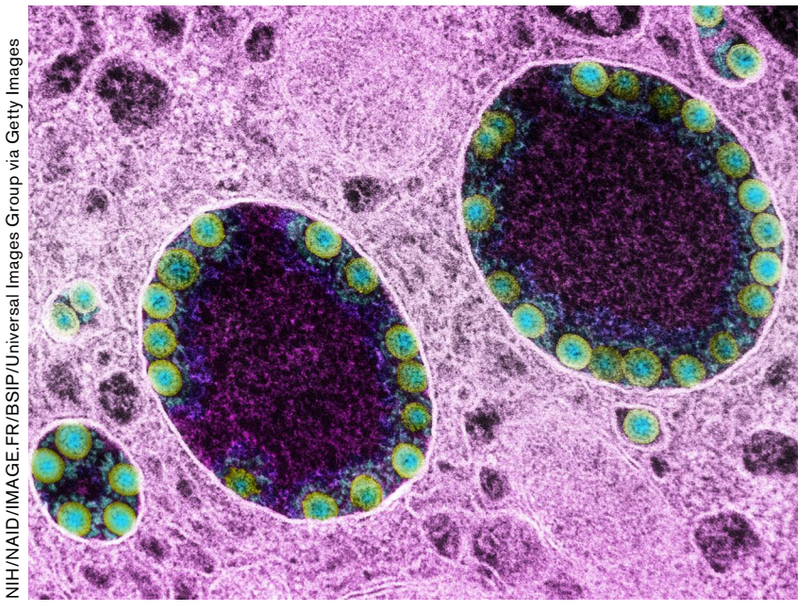

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FEATURES

OPINION

Guns Now Kill More Children and Young Adults Than Car Crashes

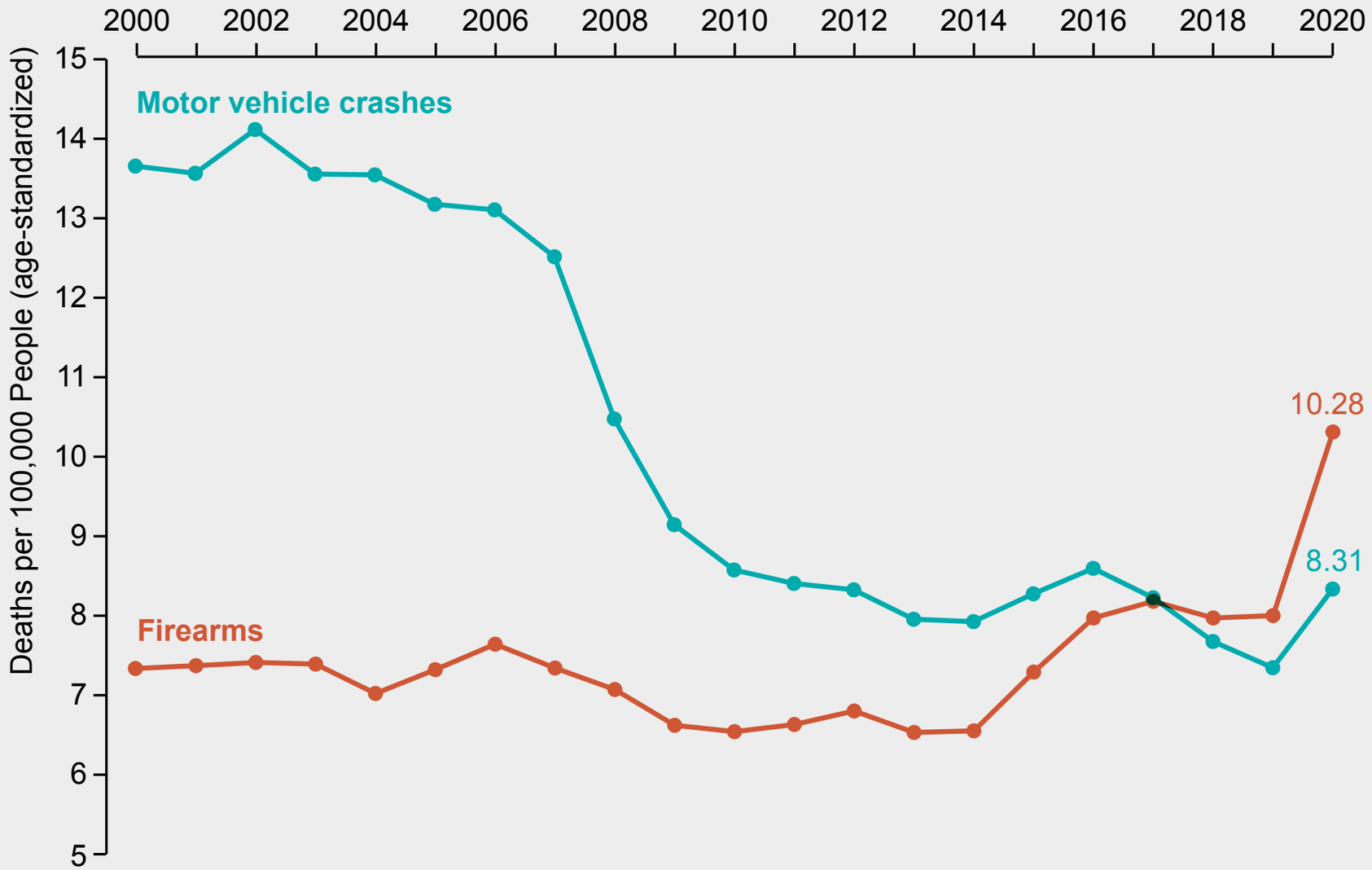
Firearms now exceed motor vehicle crashes as the leading cause of injury-related death for people ages one to 24, a new analysis shows

For much of the past few decades motor vehicle crashes were the most common cause of death from injury—the leading cause of death in general—among children, teenagers and young adults in the U.S. But now a new analysis shows that, in recent years, guns have overtaken automotive crashes as the leading cause of injury-related death among people ages one through 24.

The switchover, which happened in 2017, stems from both a reduction in vehicle-related deaths and a grim uptick in gun-related fatalities. From 2000 to 2020, the number of firearm-related deaths in the one- to-24-year-old age group increased from 7.3 per 100,000 people to 10.28 per 100,000, age-adjusted data from the Centers for Disease Control and Prevention reveal. During the same period, vehicle-related deaths declined from 13.62 to 8.31 per 100,000.

"The crossing of these trend lines demonstrates how a concerted approach to injury prevention can reduce injuries and deaths—and, conversely, how a public health problem can be exacerbated in the absence of such attention," wrote

U.S. Death Rates from Motor Vehicle Crashes and Firearms, Ages 1–24



Amanda Montañez; Sources: Web-Based Injury Statistics Query and Reporting System, Centers for Disease Control and Prevention; "Crossing Lines—A Change in the Leading Cause of Death among U.S. Children," by Lois K. Lee et al., in *New England Journal of Medicine*, Vol. 386, No. 16; April 21, 2022

Lois Lee, a senior associate in medicine at Boston Children's Hospital, and her colleagues in the recent analysis of CDC data, which was published as a Perspective piece in the *New England Journal of Medicine.*

The decline in vehicle deaths is largely the result of a concerted effort to track and study motor vehicle crashes. Congress established the National Highway Traffic Safety Administration (NHTSA) in 1970 with the goal of saving lives and preventing traffic-related injuries. One of the agency's key actions was to create and maintain a public database of automobile deaths on U.S. roads, allowing researchers to identify ways to improve safety.

In contrast, no such federal agency exists to regulate the safety of firearms—and it took decades just to develop a national database for tracking firearm deaths, Lee and her colleagues noted in their paper. Furthermore, from 1996 to 2018, a rider in a government spending bill called the Dickey Amendment effectively discouraged CDC funding for research on preventing gun injuries. It prohibited the CDC from using its funds to "advocate or promote gun control," which resulted in a freeze on gun violence research at the agency. That broadly interpreted directive was extended to the National Institutes of Health in late 2011. In 2018 Congress reinterpreted the Dickey Amendment to allow such research, and funding was finally granted in late 2019.

"There is robust funding for motor vehicle–related research and interventions," Lee says, yet "we have just begun to see federal funding for firearm research after 25 years of nearly no funding."

Lee and her colleagues credited a number of safety improvements in vehicles for saving lives among children and teens. These measures include automatic braking and side airbags, as well as booster-seat laws and graduated licensing. Although all U.S. states require that people get a license and registration to drive, a loophole in federal law allows people in many states to buy a gun from an unlicensed dealer without so much as a background check.

Federal law shields gunmakers from some liability in negligence claims, including when guns fall into the hands of children—with lethal consequences, according to Lee and her team.

Linda Degutis, a lecturer at the Yale School of Public Health and former director of the CDC's National Center for Injury Prevention and Control, says the new findings about cause-of-death trends in young people are not surprising. "We have not focused as much on interventions, on how we can keep people safe, given that there are firearms in our environment—and that includes children," says Degutis, who was not involved in the new analysis. "We have been able to decrease fatalities from motor vehicle crashes in children and in young adults, [and] we've done it by using interventions that didn't eliminate motor vehicles.... We have not focused on that same kind of strategy with guns."

Many experts assert that the high rate of gun deaths among young people is not an inevitability and that it is possible to prevent such deaths by gathering data and doing research.

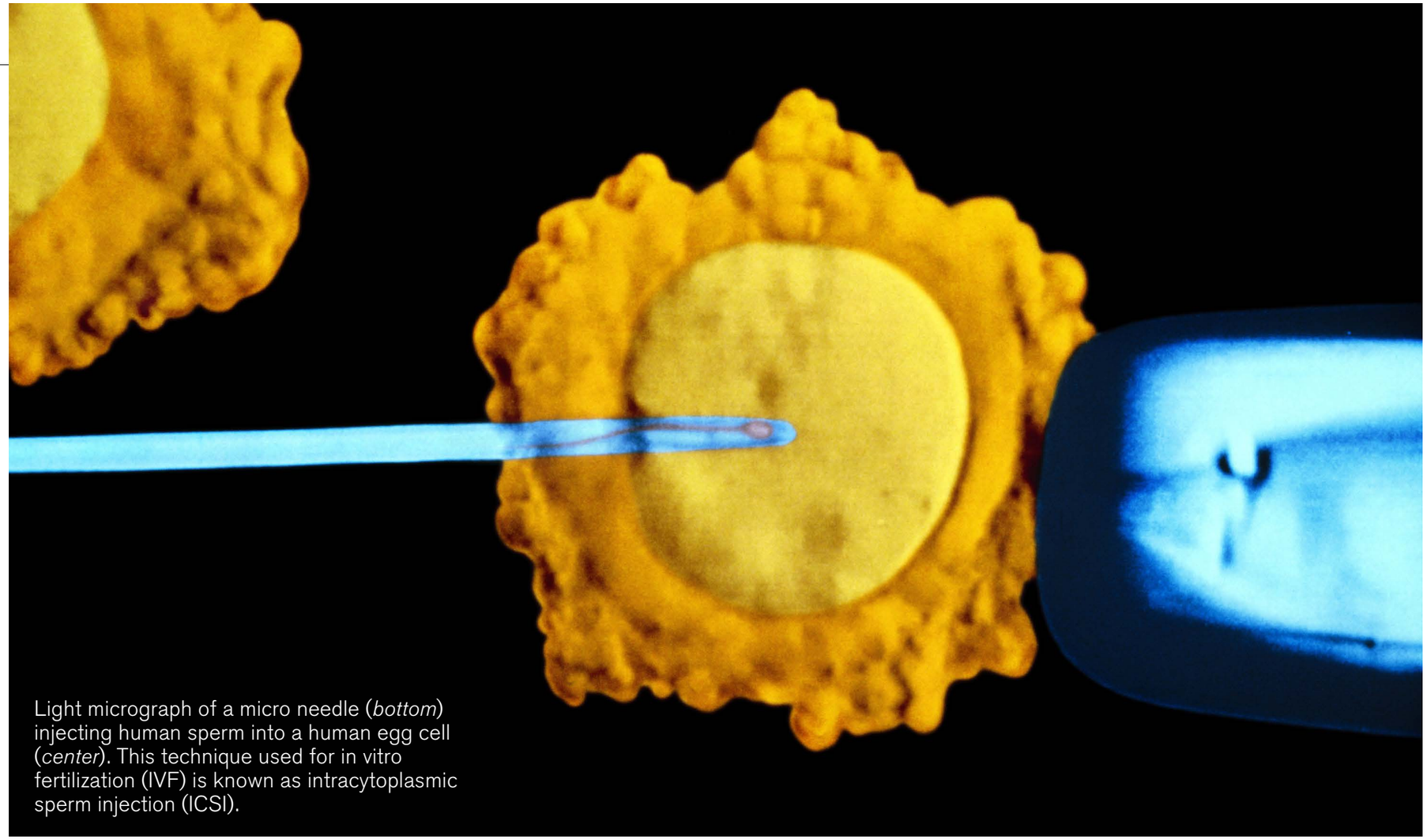
"As the progress made in reducing deaths from motor vehicle crashes shows," Lee and her colleagues wrote, "we don't have to accept the high rate of firearm-related deaths among U.S. children and adolescents." —*Tanya Lewis*

An IVF Embryo Test Aims to Prevent Miscarriages: Is It Worth It?

The test could help ensure a successful pregnancy but still leaves hopeful parents with some difficult decisions

In clinics today, fertility patients using in vitro fertilization (IVF) are routinely advised to pay for an expensive supplemental test called preimplantation genetic testing for aneuploidy (PGT-A), in which a handful of cells are removed from the embryo to examine their DNA. For those who can afford it, PGT-A is popular because it can flag genetic abnormalities that increase the odds that a pregnancy, should it occur, will end in miscarriage.

Pervasive use of the test has also generated controversy. The authors of an April 2022 study in *Human Reproduction* have sparked debate and alarmed prospective parents by suggesting that many clinics are too quick to discard embryos based on PGT-A and are ignoring a growing



Light micrograph of a micro needle (*bottom*) injecting human sperm into a human egg cell (*center*). This technique used for in vitro fertilization (IVF) is known as intracytoplasmic sperm injection (ICSI).

ARFIV/CNRI/Science Source

body of evidence that some of these embryos are capable of producing a viable pregnancy.

If all of a patient's embryos are rejected based on PGT-A results, they may lose their only chance at taking home a baby or be directed prematurely toward expensive alternative technologies such as donor eggs that would deprive them of a child genetically related to both parents. In a quote in a 2017 article in *New York Magazine*'s The Cut, study co-author Norbert Gleicher of the Center for Human Reproduction in New York City called this waste of potentially good embryos "an unprecedented scandal."

Proponents of the test have pushed back strongly on this criticism. They say that PGT-A benefits decision-making for anyone who can afford it and provides patients with realistic information on each embryo's odds of viability. PGT-A is also credited with reducing the risks and costs associated with earlier iterations of IVF.

The process of halving and then combining maternal and paternal chromosomes is a delicate operation that often goes awry, and as a result, embryos frequently have added or missing DNA—a condition known as aneuploidy, which can prevent or derail a pregnancy. Aneuploidy is well established as the most common cause of miscarriage in the first trimester and helps explain why many couples who place all their hopes on implanting a single egg each cycle are unable to have a baby. IVF uses artificial hormonal stimulation to coax the ovaries into ripening multiple eggs that are then removed and fertilized in the lab to produce as many embryos as possible. PGT-A was developed to give doctors a better basis for embryo selection than eyeballing them under a microscope, which is a hit-or-miss form of assessment that leans heavily on gut instinct.

For those patients with plenty of embryos, the advantages of PGT-A are clear. Ruling out the embryos most likely to result in miscarriage helps reduce the number of IVF cycles required to achieve a successful pregnancy. Every IVF cycle is expensive and, like miscarriage, physically and emotionally taxing. What's more, according to Teresa Cacchione, a genetic counselor at Reproductive Medicine Associates of New York, it is the use of PGT-A that has enabled a recent shift in practice in favor of transferring only a single embryo per cycle into the uterus rather than two or more. This change has radically reduced the high number of twins, triplets and higher-order multiples that for decades

represented the primary source of increased medical risk for babies conceived through IVF.

But while the rationale for use of PGT-A appears sound, research has exposed the limitations of embryo biopsy. As lead author David Barad of the Center for Human Reproduction points out, the cells biopsied are a small sample of the whole. They are pulled from the tissue that will eventually form the placenta and not the fetus itself. "If you reach down in a field full of wildflowers and close your eyes and pull up three flowers, and they're all blue, that doesn't mean the field is all blue," he says. Yet other studies have shown that PGT-A does a good job at representing the mix of cells in the embryo.

What testing has shown is that many embryos—perhaps even all—are in fact a mix of different cell lines with variations in their DNA complement. Mistakes occur as cells divide and multiply. Most of these are lethal, but surviving cells will pass down whatever changes occurred to all their daughter cells, creating a sort of alternative genetic lineage. This mix of cell lines is called mosaicism. A 2020 *American Society for Reproductive Medicine* (ASRM) paper estimated that the odds of reproductive success are inversely related to the level of mosaicism identified in an embryo.

In practice, embryos are classified as fully aneuploid rather than mosaic when more than 80 percent of the cells biopsied show one or more genetic abnormalities. Cacchione says that her facility will not transfer fully abnormal embryos at this point "because of the incredibly low likelihood of an ongoing pregnancy and the very high chance of loss." Reproductive Medicine Associates of New York will offer prospective parents the option of transferring embryos identified as mosaic, but some clinics will not, despite guidance from organizations such as ASRM that this can be done with appropriate counseling.

In their study, Barad and his co-authors transferred both mosaic and fully aneuploid embryos after patients were denied the opportunity to use them at other clinics. Their findings, in line with previous work, demonstrate that mosaic embryos are frequently capable of generating a successful pregnancy. Interestingly, in follow-up testing of a fetus or subsequent child, the rogue cell lines with added or missing DNA have often disappeared altogether.

This resilience in the embryo has taken some by surprise. Experts hypothesize that embryos can self-correct when healthy cell lines outperform the competition, pushing the aneuploid cell lines into obsolescence. "It didn't surprise me at all," says Jamie Grifo, director of the NYU Langone Fertility Center, "because we knew from earlier experience that any embryo has a shot." But long shots have high costs. Grifo posits that it might take more than 125 transfers of fully aneuploid embryos to get a single pregnancy; all of those other transfers represent failed cycles of IVF, including an estimated 35 to 40 miscarriages. Although Barad champions the use of both mosaic and fully aneuploid embryos, the differences between the two in his own data were stark: 23 mosaic embryos transferred produced six live births, whereas 79 fully aneuploid embryos produced only two.

Lurking in the background is the fear that using aneuploid or mosaic embryos could produce children with serious medical issues. Cacchione says she acknowledges the issue with patients. "We don't have long-term data," she says. "Most of the babies born from known mosaic transfers are under the age of four." But she points out that doctors were undoubtedly transferring mosaic embryos unwittingly for decades before the routine use of PGT-A, with no evidence of increased birth defects. "That's all very reassuring," Cacchione says. Still, Barad suggests, concerns about malpractice may limit clinics' willingness to allow patients to try and use any embryos deemed "abnormal." "Some institutions are being guided by their lawyers," he explains.

Barad claims that aggressive marketing of PGT-A, which typically adds $4,000 to $5,000 to the cost of IVF, may be resulting in overuse. But Cacchione contends the test is valuable for any patient who can afford it, provided it is combined with good counseling and patient education. She argues that PGT-A allows patients to weigh a realistic understanding of the chance of a successful pregnancy against the cost of repeated rounds of IVF and the physical and emotional toll associated with miscarriage. In the end, Cacchione says, "it's a very personal decision." *—Laura Hercher*

Nose Spray Vaccines Could Quash COVID Virus Variants

Three nasal spritzes, now in advanced trials, could trigger stronger immunity than shots in the arm

The relentless evolution of the COVID-causing coronavirus has taken a bit of the shine off the vaccines developed during the first year of the pandemic. Versions of the virus that now dominate circulation—Omicron and its subvariants—are more transmissible and adept at evading the body's immune defenses than its original form. The current shots to the arm can still prevent serious illness, but their ability to ward off infection completely has been diminished. And part of the reason may be the location of the jabs, which some scientists now want to change.

To block infections entirely, scientists want to deliver inoculations to the site where the virus first makes contact: the nose. People could simply spray the vaccines up their nostrils at home, making the preparation much easier to administer. There are eight of these nasal vaccines in clinical development now and three in phase 3 clinical trials, where they are being tested in large groups of people. But making these vaccines has proved to be slow-going because of the challenges of creating formulations for this unfamiliar route that are both safe and effective.

What could be most important about nasal vaccines is their ability to awaken a powerful bodily defender known as mucosal immunity, something largely untapped by the standard shots. The mucosal system relies on specialized cells and antibodies within the mucus-rich lining of the nose and other parts of our airways, as well as the gut. These elements move fast and arrive first, stopping the virus, SARS-CoV-2, before it can create a deep infection. "We are dealing with a different threat than we were in 2020," says Akiko Iwasaki, an immunologist at Yale University. "If we want to contain the spread of the virus, the only way to do that is through mucosal immunity."

Iwasaki is leading one of several research groups in the U.S. and elsewhere that are working on nasal vaccines. Some of the sprays encapsulate the coronavirus's spike proteins—the prominent molecule that the virus uses to bind to human cells—into tiny droplets that can be puffed into the sinuses. Others add the gene for the spike to harmless versions of common viruses, such as adenoviruses, and use the defanged virus to deliver the gene into nasal tissue. Still others rely on synthetically bioengineered SARS-CoV-2 converted into a weakened form known as a live attenuated vaccine.

The more familiar shots in the arm

Dzmitry Kliapitski/Alamy Stock Photo

create a type of immune response known as systemic immunity, which produces what are called immunoglobulin G (IgG) antibodies. They circulate throughout the bloodstream and patrol for the virus. Nasal sprays assemble a separate set of antibodies known as immunoglobulin A (IgA). These populate the spongy mucosal tissues of the nose, mouth and throat, where the COVID-causing coronavirus first lands. Iwasaki likens mucosal vaccines to putting a guard at the front door, as opposed to waiting until the invader is already inside to attack.

Whereas conventional injectable vaccines are generally poor at inducing protective mucosal immunity, nasal vaccines have been shown to do a good job of triggering both mucosal and systemic responses. Last year researchers at the National Institutes of Health conducted a side-by-side comparison of intranasal and intramuscular delivery of the Oxford-AstraZeneca vaccine. They found that hamsters that had received the vaccine through the nose had higher levels of antibodies against SARS-CoV-2 in their blood than those who received it through the muscle. The University of Oxford is now testing intranasal vaccination in a phase 1 trial, which will assess the safety of the vaccine in a small number of people.

Developing a nasal vaccine is tricky, however, because scientists know relatively little about the machinations of mucosal immunity. "While the human immune system is a black box, the mucosal immune system is probably the blackest of the black boxes," says epidemiologist Wayne Koff, CEO and founder of the Human Vaccines Project, a public-private partnership aimed at accelerating vaccine development.

What scientists do know is making them tread cautiously. Because of the nose's proximity to the brain, substances squirted up the nasal passages could raise the risk of neurological complications. In the early 2000s a nasal flu vaccine licensed and used in Switzerland was linked to Bell's palsy, a temporary facial paralysis. "Since then, people have become a little bit nervous about a nasal vaccine," Iwasaki says.

And although a spray seems like an easier delivery method than a shot, in practice that is not the case. With intramuscular injections, a needle delivers the vaccine ingredients directly into the muscle, where they quickly encounter resident immune cells. Sprays, in contrast, must make their way into the nasal cavity without being sneezed out. Then those ingredients have to breach a thick barrier gel of mucus and activate the immune cells locked within. Not all do. One company, Altimmune, stopped development of its COVID nasal vaccine AdCOVID after disappointing early trial results.

Weakened or attenuated viruses can get through the barrier to infect cells, so some vaccine developers are turning to them. Two companies, Meissa Vaccines and Codagenix, have used synthetic biology to build an attenuated version of the novel coronavirus containing hundreds of genetic changes that drastically reduce its ability to replicate. In a recent news release, the Codagenix team reported promising results of its vaccine, CoviLiv, in a phase 1 trial. The spray induced a strong immune response against proteins shared by different variants of SARS-CoV-2, including the recent Omicron subvariant BA.2. That is because the vaccine trains the immune system to recognize all the viral proteins, not just the spike. Presenting all components of the virus makes the vaccine less vulnerable to the whims of evolution that might alter a few proteins beyond recognition. "The beauty of live attenuated vaccines is that they can provide broad long-term immunity in a very resistant context," says J. Robert Coleman, a virologist and the company's co-founder. CoviLiv is moving on to advanced testing in people as part of the World Health Organization–sponsored Solidarity Trial Vaccines, a giant randomized controlled trial of several new COVID vaccines.

For each of the candidates that have made it into clinical trials, there are several more in preclinical development. In research with mice at Yale, Iwasaki has devised a nasal spray that works as a booster to the standard intramuscular shot. The strategy, which she calls "Prime and Spike," starts with an injection of an mRNA or other COVID vaccine based on the spike protein, and this triggers an initial immune response. Then researchers spray a mix with similar spike proteins directly into the nose, converting that first reaction into mucosal immunity. In a preprint study not yet published in a peer-reviewed scientific journal,

her team found that their one-two-punch protected mice from severe COVID while also significantly reducing the amount of SARS-CoV-2 in the nose and lungs.

When the researchers added spike proteins from the coronavirus that created a global outbreak in 2003—SARS-CoV-1—to their spray, they found that it induced a broad spectrum of antibodies. The combination has the potential to defend against new coronavirus strains or variants. "There is a big push for a universal coronavirus vaccine," Iwasaki says. "We can get there, and as a bonus we can provide mucosal immunity." She has licensed the technology to Xanadu Bio, a company she co-founded, and is currently seeking funding to launch human trials.

With no needles or syringes, nasal inoculations could reach a lot more people, and that could prove to be a big advantage. Koff, however, thinks the real deciding factor will be whether tests prove these vaccines stop infections and illness, and those results will be more important than ease of use. "At the end of the day, efficacy is going to trump everything," he says.

—Marla Broadfoot

This Tick Can Make You Allergic to Meat, and It's Spreading

Work on genetically modified pigs might provide a solution to the strange illness

Kristina Carlson didn't think much about the tick she pulled off her torso while she was hiking in the mountains of North Carolina in September 2020. But back home in Mississippi a month later, Carlson complained to her doctor of aching joints and a bloated feeling in her stomach. Her doctor ruled out rheumatoid arthritis, and a blood test didn't turn up anything definitive. Then Carlson started having eye infections. In February 2021 she suddenly found a strange rash on her face; an urgent-care facility doctor treated her for shingles, but the rash didn't get better.

When she returned to her doctor's office, a nurse practitioner asked, "Do you remember having a tick bite?" This led to another blood test that revealed antibodies associated with alpha-gal, a sugar found in the meat and fat of nonprimate mammals.

Lone star tick (*Amblyomma americanum*)

Jason Ondreicka/Alamy Stock Photo

Alpha-gal syndrome (AGS) is an allergic reaction that can arise after someone is bitten by a lone star tick. Named for the white dot on the back of adult females, the ticks are historically located in the south-central and southeastern U.S. They transmit the alpha-gal molecule from mammals they've fed on to people they bite.

Now the ticks are being found in New Jersey and New York State's Long Island, with sporadic reports farther north along the Eastern Seaboard and in parts of the Midwest. The spread is prompting researchers to consider the potential long-term complications of AGS and to further verify the cause of the allergy using genetically modified meat.

Normally when a person eats meat from nonprimate mammals, such as cows and pigs, their body does not react to alpha-gal. But when a tick bite introduces the molecule, the

immune system recognizes it as an invader and produces antibodies known as immunoglobulin E (IgE) tailored against it. IgE antibodies attach to disease-fighting white blood cells called basophils in the bloodstream and mast cells in tissues. The next time those cells come into contact with alpha-gal from any source, including meat, the antibodies recognize it, and the immune system attacks it.

Forming IgE "can be thought of as loading the gun," explains Scott Commins, associate chief for allergy and immunology at the University of North Carolina School of Medicine and a leading AGS researcher. "Eating mammalian meat subsequently pulls the trigger."

The resulting allergic reactions, which typically begin two to six hours after ingesting alpha-gal, vary from person to person. They can be as mild as a tingling in the mouth or as extreme as anaphylactic shock. Some people with AGS can eat a double cheeseburger and experience only light itching of their palms or scattered hives. Others who consume a trace amount of pork fat in refried beans can go into full anaphylaxis. After eating meat, Carlson would immediately experience tingling and sometimes sores in her mouth. Within 24 hours, she would often suffer eye irritation, joint inflammation, rashes on different parts of her body and swelling in her left arm.

There is currently no treatment or antidote for AGS itself. Epinephrine is the first-line treatment for anaphylaxis, and some other allergic reactions can be managed with medications, including antihistamines and corticosteroids. People with the condition have to try their best to avoid any triggering foods. Eliminating mammalian meat and other products typically allows the symptoms to clear. "I cut all the hoofed animal products," Carlson says, "and the rash, the infection, the joint [pain], the inflammation all went away."

One consolation for Carlson and most of the 34,000 other Americans diagnosed with AGS is that the meat sensitivity does not appear to be permanent and often resolves in four to five years. That's because the immune system cells that create the IgE response are immature B cells called plasmablasts. These cells, according to Commins, do not seem to convert to long-term immune memory cells that remain on the lookout during a person's entire life—the way immune memory cells triggered by certain vaccines watch for invaders for decades.

People who spend a lot of time outdoors, such as park rangers and land surveyors, might get repeated tick bites, however. "Those patients seem to develop long-lived memory cells," Commins says. "For them, unfortunately, the alpha-gal allergy probably is permanent."

As the prevalence of lone star ticks increases, however, AGS cases are expected to rise. "The ticks do appear to be spreading," says Richard S. Ostfeld, a disease ecologist and a distinguished senior scientist at the Cary Institute of Ecosystem Studies. "Unfortunately, the U.S. doesn't have any kind of nationwide active tick-surveillance program." Spotty records suggest the lone star ticks' range is expanding, he says, "but we lack high-quality rigorous data on where they are and how quickly they're moving."

Why they are spreading is also hard to pin down. The main hypothesis involves climate change, but researchers are hesitant to make that conclusion because it is difficult to test rigorously. "There are studies that suggest that as the climate continues to warm, the geographical range of the lone star tick will not expand," Ostfeld says, "although most studies suggest that it will."

What is clear is that a changing climate is lengthening the active season for at least some ticks, raising the chance that people will cross paths with these arachnids in general. For black-legged ticks in New York State, Ostfeld says, "we've demonstrated that both the larval and the nymphal stages have been appearing earlier and earlier as the climate warms. To the extent that lone star ticks behave similarly, you would expect that their active season would get longer."

Lone star ticks are less than an eighth of an inch long and very aggressive. Often found in large groups, they can detect the heat and carbon dioxide given off by humans from a couple of yards away. Then "they kind of hunt you down," Ostfeld says. "They actually run at you."

Researchers would like to find out if alpha-gal IgE might contribute to or exacerbate other conditions. In a small 2018 study, Commins and his colleagues associated the antibody with unstable plaques in coronary arteries.

In a larger 2022 study that Commins was not part of, researchers associated heart attacks with a positive blood test for alpha-gal allergy. "We're trying to understand if this alpha-gal immune response is part of a larger picture," he says.

Commins is also talking with a biotechnology subsidiary of United Therapeutics called Revivicor, which raises pigs to provide organs for transplant into humans. The animals are genetically modified to be free of alpha-gal because the sugar also causes the human body to reject pig organs. In 2020 the U.S. Food and Drug Administration approved the meat of these "GalSafe" pigs for consumption. For the past few months Revivicor has been sending the meat to people who suffer from the allergy, and it is considering a mail-order business.

Commins would like to test people who eat GalSafe pig meat. If the alpha-gal molecule has been eliminated but the people still react to the meat, researchers would have to reconsider the apparent cause of AGS. "We're confident that it's alpha-gal," Commins says, "but I think this would really prove it."

—*Sara Goudarzi*

What We Know about the Rise in Monkeypox Cases Worldwide

It is unclear how some people recently diagnosed with the disease became infected with the monkeypox virus or how it is likely to spread

More new human cases of monkeypox have been identified worldwide, with dozens reported in the U.K. alone. The increase comes after previous evidence had suggested there was unknown transmission of the monkeypox virus within the country's population, according to the U.K. Health Security Agency (UKHSA). Monkeypox is thought to originate in rodents in Central and West Africa, and it has repeatedly jumped to humans. Cases outside Africa are rare and have so far been traced to infected travelers or imported animals.

On May 7 reports surfaced that a person who had traveled to the U.K. from Nigeria had contracted monkeypox. A week later authorities reported two additional cases in London that were apparently unrelated to the first one. At least four of the people recently identified as having the disease also had no known contact with the three previous cases—this suggests unknown chains of infection in the population.

According to the World Health Organization, all of the infected people in the U.K. contracted the West African clade of the virus, a version that tends to be mild and usually resolves without treatment. The infection begins with fever, headache, aching limbs and fatigue. Typically, after one to three days, a rash develops, along with blisters and pustules that resemble those caused by smallpox, which eventually crust over.

"This is an evolving story," says Anne Rimoin, a professor of epidemiology at the University of California, Los Angeles's Fielding School of Public Health. Rimoin, who has spent many years studying monkeypox in the Democratic Republic of the Congo, has many questions: At what point in the disease process are the people who were infected? Are these really new cases or older ones that have just now been discovered? How many of them are primary cases—infections traced to contact with animals? How many of them are secondary, or human-to-human, cases? What are the infected people's travel histories? Are there connections between these cases? "I think that it's too early to make any kind of definitive statements," Rimoin says.

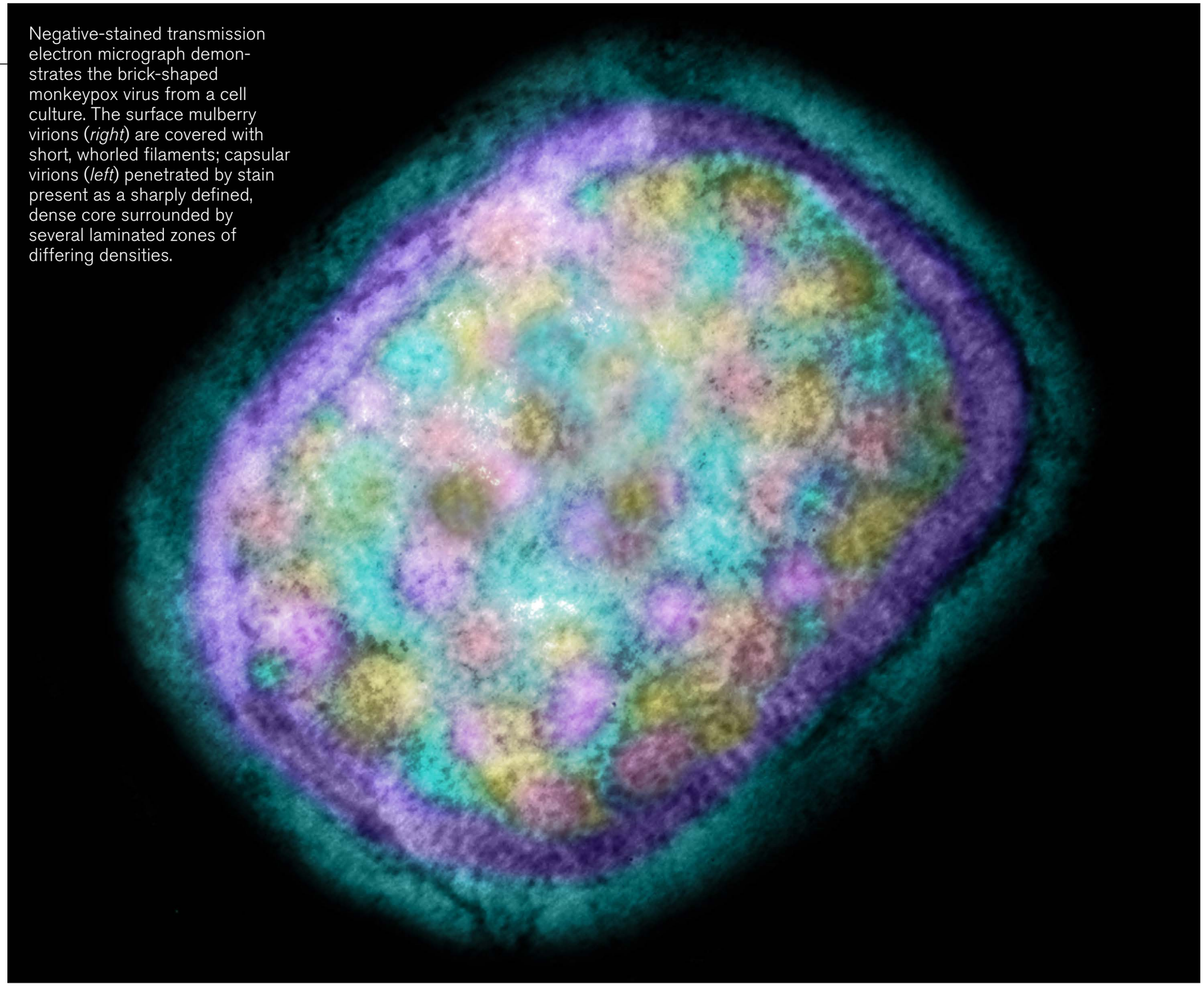
ALL REPORTED INFECTIONS INVOLVE A MILD VERSION

Many of the infected people in the U.K. are men who have sex with men and contracted the disease in London, the UKHSA reports. Some experts think transmission may be occurring in this community but could also be spread by close contact with others, including household members or health-care workers, for example. The virus spreads through droplets from the nose or mouth. It can also be transmitted via body fluids, such as from pustules, as well as objects that have come into contact with them. Most experts say close contact is necessary for infection, however.

The cluster of cases in the U.K. is rare and unusual, says Susan Hopkins, the UKHSA's chief medical

adviser. The agency is now tracking the contacts of those infected. Although data from the Democratic Republic of the Congo in the early 1980s and mid-2010s suggest the effective reproduction numbers at those times were 0.3 and 0.6, respectively—meaning each infected person passed the virus to fewer than one person in those populations, on average—there is growing evidence it can spread persistently from person to person under certain conditions. For reasons that are still unclear, the number of infections and outbreaks is increasing significantly—which is why monkeypox is considered a potential global threat.

With the situation still evolving, experts have not immediately raised concerns about widespread international outbreaks. "I'm not all that worried" about the possibility of a larger epidemic in Europe or North America, says Peter Hotez, dean of the National School of Tropical Medicine at the Baylor College of Medicine. Historically, the virus has mostly been transmitted from animals to people, and person-to-person transmission usually requires close or intimate contact. "It's not anything nearly as transmissible as COVID,



Negative-stained transmission electron micrograph demonstrates the brick-shaped monkeypox virus from a cell culture. The surface mulberry virions (*right*) are covered with short, whorled filaments; capsular virions (*left*) penetrated by stain present as a sharply defined, dense core surrounded by several laminated zones of differing densities.

Science Source

for instance, and not even as transmissible as smallpox," Hotez says.

The bigger issue, he says, is that the virus crossed over from animals—possibly rodents—in the Democratic Republic of the Congo, Nigeria and western Africa. "If you look at some of our most troublesome infectious disease threats—whether [they are] Ebola or Nipah or coronaviruses like [those that cause] SARS and COVID-19 and now monkeypox—

these are disproportionately zoonotic diseases, diseases transmitted from animals to humans," Hotez adds.

The proportion of infected people who die from monkeypox is unclear because data are poor. Known risk groups are immunocompromised people and children, and infection during pregnancy can lead to miscarriage. For the Congo Basin clade of the virus, some sources indicate mortality rates of 10 percent or greater, although more recent surveys show case mortalities lower than 5 percent. In contrast, nearly all individuals infected with the West African version survive. Seven people died during the largest known outbreak, which began in Nigeria in 2017, and at least four of them had a weakened immune system.

There is currently no specific medication for monkeypox itself, but the antiviral drugs cidofovir, brincidofovir and tecovirimat may be used. (The latter two are approved for treating smallpox in the U.S.) Healthcare workers treat the symptoms and try to prevent additional bacterial infections that can sometimes cause problems during such viral diseases. Very early in monkeypox's course, the illness can be mitigated by administering a vaccine for both monkeypox and smallpox or an antibody preparation obtained from vaccinated individuals. The U.S. recently ordered millions of vaccine doses, which will be manufactured in 2023 and 2024.

MONKEYPOX IS BECOMING MORE COMMON

The number of cases in the U.K., along with evidence of ongoing transmission among people outside Africa, provides the latest indication that the virus is changing its behavior. A study by Rimoin and her colleagues showed the rate of cases in the Democratic Republic of the Congo may have increased 20-fold between the 1980s and mid-2000s. And the virus has resurfaced in several West African countries years later: in Nigeria, for example, there have been more than 550 suspected cases since 2017, of which more than 240 were confirmed, including eight deaths.

It remains a mystery why more people in Africa are now contracting the virus. The factors that contributed to recent Ebola epidemics, which infected several thousand people in West Africa and the Democratic Republic of the Congo, may play a role. Experts suggest that factors such as population growth and more settlements near forests, as well as increasing interaction with potentially infected animals, favor the transmission of animal viruses to humans. At the same time, viruses spread faster in general because of higher population density, better infrastructure and more travel, possibly leading to international outbreaks.

The spread of monkeypox in West Africa could also indicate that the virus has appeared in a new animal reservoir. The virus can infect a whole range of animals, including many kinds of rodents, monkeys, pigs and anteaters. Infected animals transmit it relatively easily to other types of animals and humans—which is what happened in the first outbreak outside Africa. In 2003 the virus entered the U.S. with African rodents, and these in turn infected prairie dogs that were sold as pets. Dozens of people in the country became infected with monkeypox in that outbreak.

ON THE TRAIL OF SMALLPOX

The factor presumed most important in the current spate of monkeypox cases, however, is that population-wide vaccination coverage against smallpox is declining around the world. Smallpox vaccination reduces the likelihood of contracting monkeypox by about 85 percent. Since the end of the smallpox vaccination campaign, however, the proportion of unvaccinated people has been steadily increasing, making it easier for monkeypox to infect humans. Thus, the share of human-to-human transmissions among all infections has risen from about one third in the 1980s to three quarters in 2007. Another factor pointing to reduced vaccinations is that the average age of those infected with monkeypox has increased with the amount of time since the smallpox vaccination campaign ended.

Experts in Africa have warned that monkeypox could change from a regionally widespread zoonosis to a globally relevant infectious disease. The virus may be filling the ecological and immunological niche once occupied by the smallpox virus, wrote Malachy Ifeanyi Okeke of the American University of Nigeria and his colleagues in a 2020 paper.

"Currently there is no global system in place to manage the spread of monkeypox," said Nigerian virologist Oyewale Tomori in an interview published in the *Conversation* last

year. But it is considered highly unlikely that the current outbreak will become an epidemic in the U.K. The risk to the population is so far low, according to the UKHSA. Now the agency is looking for more cases and working with partners internationally to find out if there are similar clusters of monkeypox in other countries.

"Once we've identified the cases, then we're going to have to do really thorough case investigations and contact tracing—and then also do some sequencing to really crack down how this virus has been spreading," Rimoin says. It is possible the virus had been circulating for some time before public health authorities took notice. "If you shine a flashlight in the dark," she says, "you're going to see something."

Until scientists understand how the virus is transmitting, Rimoin adds, "we have to go on what we know already but also be humble—and remember that these viruses are always capable of changing and evolving."

—Lars Fischer and Tanya Lewis

A version of this article originally appeared in Spektrum der Wissenschaft *and was reproduced with permission.*

Universal Health Care Could Have Saved More Than 338,000 U.S. Lives during COVID

The numbers of lives lost and dollars spent would have been significantly lower if coverage had been extended to everyone, a new study says

Americans spend more on health care than people in any other nation. Yet in any given year, the piecemeal nature of the American medical insurance system causes many preventable deaths and unnecessary costs. Not surprisingly, COVID-19 only exacerbated this already dire public health issue, as evidenced by the U.S.'s elevated mortality, compared with that of other high-income countries.

A new study quantifies the severity of the impact of the pandemic on Americans who did not have access to health insurance. According to findings published in the *Proceedings of the National Academy of Sciences USA*, from the pandemic's beginning until mid-March 2022, universal health care could have saved more than 338,000 lives from COVID-19 alone. The U.S. also could have saved $105.6 billion in health-care costs associated with hospitalizations from the disease—on top of the estimated $438 billion that could be saved in a nonpandemic year.

"Health-care reform is long overdue in the U.S.," says the study's lead author Alison Galvani, who is director of the Center for Infectious Disease Modeling and Analysis at the Yale School of Public Health. "Americans are needlessly losing lives and money."

People who do not have insurance usually do not have a primary care doctor, which means they are more likely to suffer from preventable diseases such as type 2 diabetes. They also tend to wait longer to see a doctor when they fall ill. These two factors already contribute to higher mortality rates in nonpandemic years, and they compounded the impacts of COVID-19. Comorbidities exacerbate the risk of the disease, and waiting to seek care increases the likelihood of transmission to other people.

Prior to the pandemic, 28 million American adults were uninsured, and nine million more lost their insurance as a result of unemployment because of COVID. "Many Americans feel secure in having good health insurance from their employer, but employer-based insurance can be cut off when it is needed most," Galvani points out.

In the new study, Galvani's team compared the mortality risks of COVID-19 among people with and without insurance, as well as their risks of all other causes of death. The researchers compiled population characteristics of all uninsured Americans during the pandemic, taking into account things such as age-specific life expectancy and the elevation in mortality associated with a lack of insurance. They calculated that 131,438 people in total could have been saved from dying of COVID in 2020 alone. And more than 200,000 additional deaths from COVID could have been averted since then, bringing the total through March 12, 2022, to more than 338,000.

The researchers also estimated the cost to insure the entire American population—and the savings that measure would produce. They found that a single-payer health-care system would generate savings

A woman walks among a field of some 660,000 white flags representing the number of U.S. lives lost to COVID-19 at the National Mall in Washington, D.C., on September 16, 2021.

Rod Lamkey/CNP/Sipa USA/Alamy Stock Photo

in three ways: more efficient investment in preventive care, lowered administrative costs and increased negotiating power for pharmaceuticals, equipment and fees. This would ultimately produce a net savings of $459 billion in 2020 and $438 billion in a nonpandemic year, the authors found. "Medicare for All would be both an economic stimulus and lifesaving transformation of our health-care system," Galvani says. "It will cost people far less than the status quo."

Galvani and her colleagues' findings are "very convincing," and "the methodology strikes me as exactly right," says Robert Reich, a professor of public policy at the University of California, Berkeley, who was not involved in the work. "The savings estimates are consistent with every other estimate I've seen."

Ann Keller, an associate professor of health policy and management also at U.C. Berkeley, suspects, however, that the new study likely underestimates the deaths that could have been avoided through universal health care because it does not consider the lower rates of chronic disease that often accompany single-payer systems. "Having consistent access to care can prevent chronic disease from occurring and can ensure that patients who develop chronic disease have it better managed," says Keller, who was also not involved with the research. "I would think that, if one took that into account, the estimates of avoided deaths would be greater than the numbers reported here."

Whatever the exact figures, Galvani says the message that comes out of the new study is clear: "Universal single-payer health care is both economically responsible and morally imperative." —*Rachel Nuwer*

SARS-CoV-2 particles (*green*) in infected olfactory epithelial cells

NIH/NIAID/IMAGE.FR/BSIP/Universal Images Group via Getty Images

Chronic Covid: The Evolving Story

When SARS-CoV-2 lingers in the body, it accumulates many of the same mutations seen in the most dangerous global variants. What can scientists do with this knowledge?

By Ewen Callaway

Ewen Callaway is a senior reporter at *Nature*.

VIROLOGIST SISSY SONNLEITNER tracks nearly every COVID-19 case in Austria's rugged eastern Tyrol region. So when one woman there kept testing positive for months on end, Sonnleitner was determined to work out what was going on.

Before becoming infected with SARS-CoV-2 in late 2020, the woman, who was in her 60s, had been taking immune-suppressing drugs to treat a lymphoma relapse. The COVID infection lingered for more than seven months, causing relatively mild symptoms, including fatigue and a cough.

Sonnleitner, who is based at a microbiology facility in Außervillgraten, Austria, and her colleagues collected more than two dozen viral samples from the woman over time and found through genetic sequencing that it had picked up about 22 mutations. Roughly half of them would be seen again in the heavily mutated Omicron variants of SARS-CoV-2 that surged around the globe months later. "When Omicron was found, we had a great moment of surprise," Sonnleitner says. "We already had those mutations in our variant."

Omicron did not arise from the woman's infection, which doesn't seem to have spread to anyone. And although no definitive links have been made to individual cases, chronic infections such as hers are a leading candidate for the origins of Omicron and other variants that have driven COVID surges globally. "I don't think there can be any doubt in anyone's mind that these are a source of new variants," says Ravindra Gupta, a virologist at the University of Cambridge.

Researchers want to understand how the virus might evolve the ability to spread from person to person more easily, to evade the immune response, or to become more or less severe. Some or all of these qualities might be forged during the course of a chronic infection. "We don't quite understand what can evolve in a single individual—and what cannot," says Alex Sigal, a virologist at the Africa Health Research Institute in Durban, South Africa.

The odds are remote that this knowledge could help to predict the next deadly strain or even to trace variants such as Omicron to their origin. Still, virologists hope that by improving their understanding of viral evolution, they will be able to anticipate what future variants might look like—and potentially find better ways to treat chronic infections. "It's such an important problem, given that we don't want another variant that we can't handle," Sigal says.

DEADLY COMPETITION

Since late 2019 scientists have sequenced the genomes of more than 11 million samples of SARS-CoV-2 taken from people. These efforts have drawn an evolutionary tree that is remarkable in its breadth, showing how the virus has changed during its march around the planet, gaining just a couple of stable mutations per month as it moves from person to person.

"But that's only one part of the evolutionary story," says Sarah Otto, an evolutionary biologist at the University of British Columbia. Each person's infection is its own universe, where new mutations arise as the infection spreads from cell to cell. Most of these changes won't matter to the virus, and many will do it harm. But some might give it a slight advantage over other versions of the virus in that person's body, enhancing its ability to spread or providing some resistance to immune defences. These two traits—infectivity and immune evasion—are the main ways in which SARS-CoV-2 has evolved since it first emerged in 2019.

In acute SARS-CoV-2 infections, which generally last a week or two before being cleared by the immune system, versions of the virus with advantageous mutations have little time to outcompete those that lack them. The odds of a virus with such an advantage being transmitted to another individual are therefore small. Studies suggest that only a few virus particles—maybe even just one—are needed to seed a new infection. "Which of those viruses happens to be in the aerosol droplet you sneeze out at the time someone walks by and breathes in is largely a matter of luck," says Jesse Bloom, a evolutionary biologist at the Fred Hutchinson Cancer Center in Seattle. "So most of the beneficial mutations that have arisen in a patient are lost, and then evolution has to start up all over again."

This "transmission bottleneck" is the reason SARS-CoV-2 picks up around two mutations per month globally, on average. But in chronic infections, which last for weeks to months, viruses with advantageous mutations have time to outcompete others.

Compared with acute cases, these long-term infections also allow time for much more viral diversity to develop.

And through a process called recombination, which can shuffle the genomes of SARS-CoV-2 particles together, mutations that are beneficial in one part of the body, such as the upper airways, might show up in viruses bearing other useful properties, says Andrew Rambaut, an evolutionary biologist at the University of Edinburgh. “If the result is a fitter virus, it can suddenly take off.”

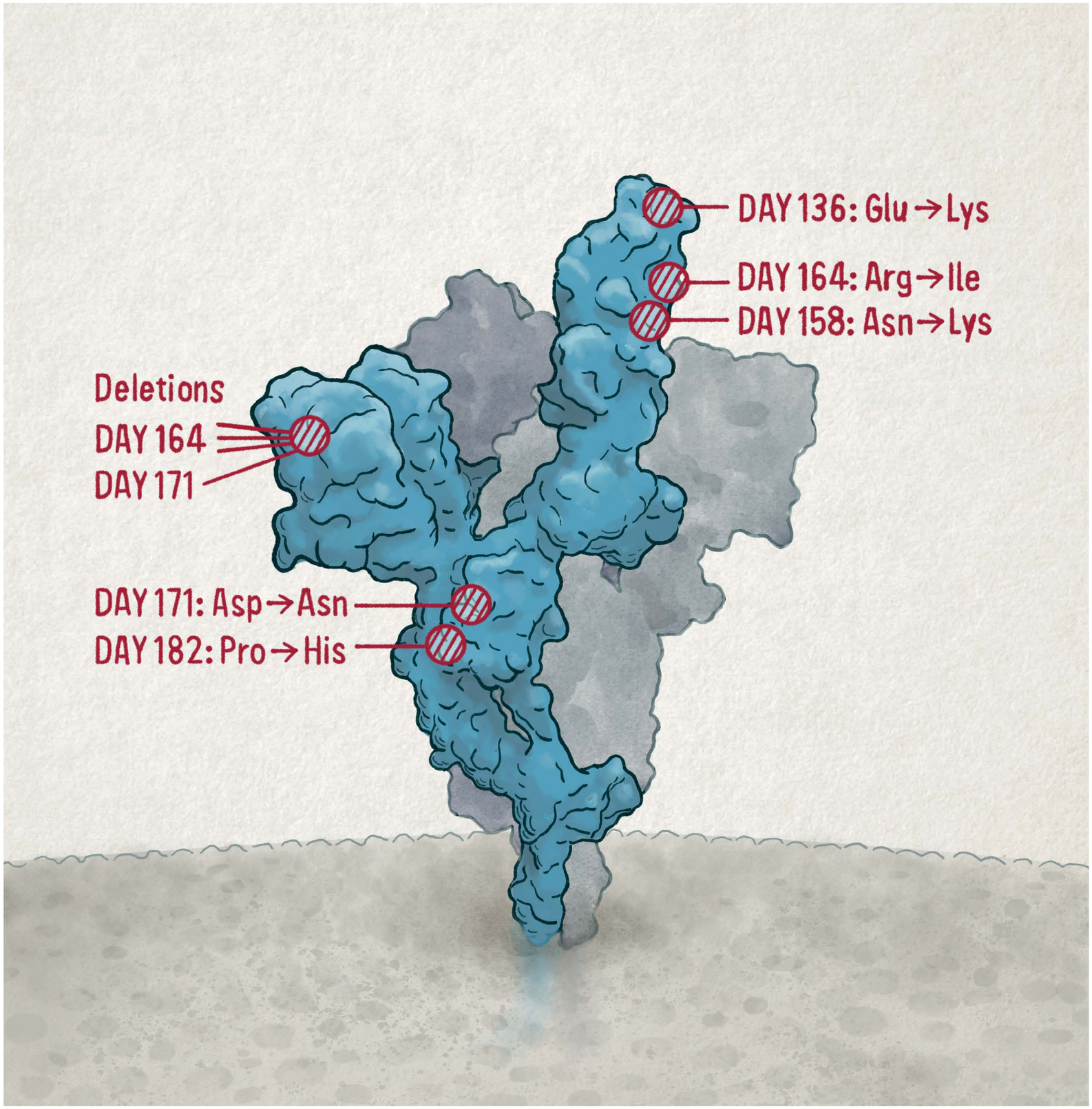
As a result of chronic infections, globally “this virus has opportunities not just to evolve in one way, in one direction, but literally thousands, maybe tens of thousands, of directions over months,” Otto says.

TARGETING SPIKE

No two chronic infections are identical. But in dozens of case reports, researchers have begun to identify common signatures of long-term infection. One of the most striking, Otto says, is the large number of amino acid changes that accrue in the virus’s spike protein, which helps it to infect cells and is a primary target for the body’s immune response.

Many of these mutations map to regions of the spike that are targeted by antibodies, such as its receptor binding domain (RBD) and the N-terminal domain, which are involved in recognizing and infecting host cells. This makes sense, says Darren Martin, an evolutionary virologist at the University of Cape Town in South Africa. If a person’s immune system fails to clear an infection fully, the surviving viruses are likely to bear immunity-evading mutations that helped them to survive the attack. One study, which has not been peer-reviewed, found that the most common mutation in chronic infections is at a position in the spike protein’s RBD called E484. Changes at this site can prevent some potent infection-blocking antibodies from attaching to the virus.

Some mutations don’t work particularly well on their own. Last year Gupta and his team described a 102-day infection in a man in his 70s who had a compromised



These are mutations that accumulated in the spike protein of SARS-CoV-2 during a seven-month-long infection.

Illustration by Nik Spencer/*Nature*

immune system and who ultimately died from the infection. After doctors had treated him with convalescent plasma—the antibody-containing portion of blood donated by people who had recovered from COVID—Gupta's team found that viruses with a pair of spike-protein mutations were thriving in the man's airways.

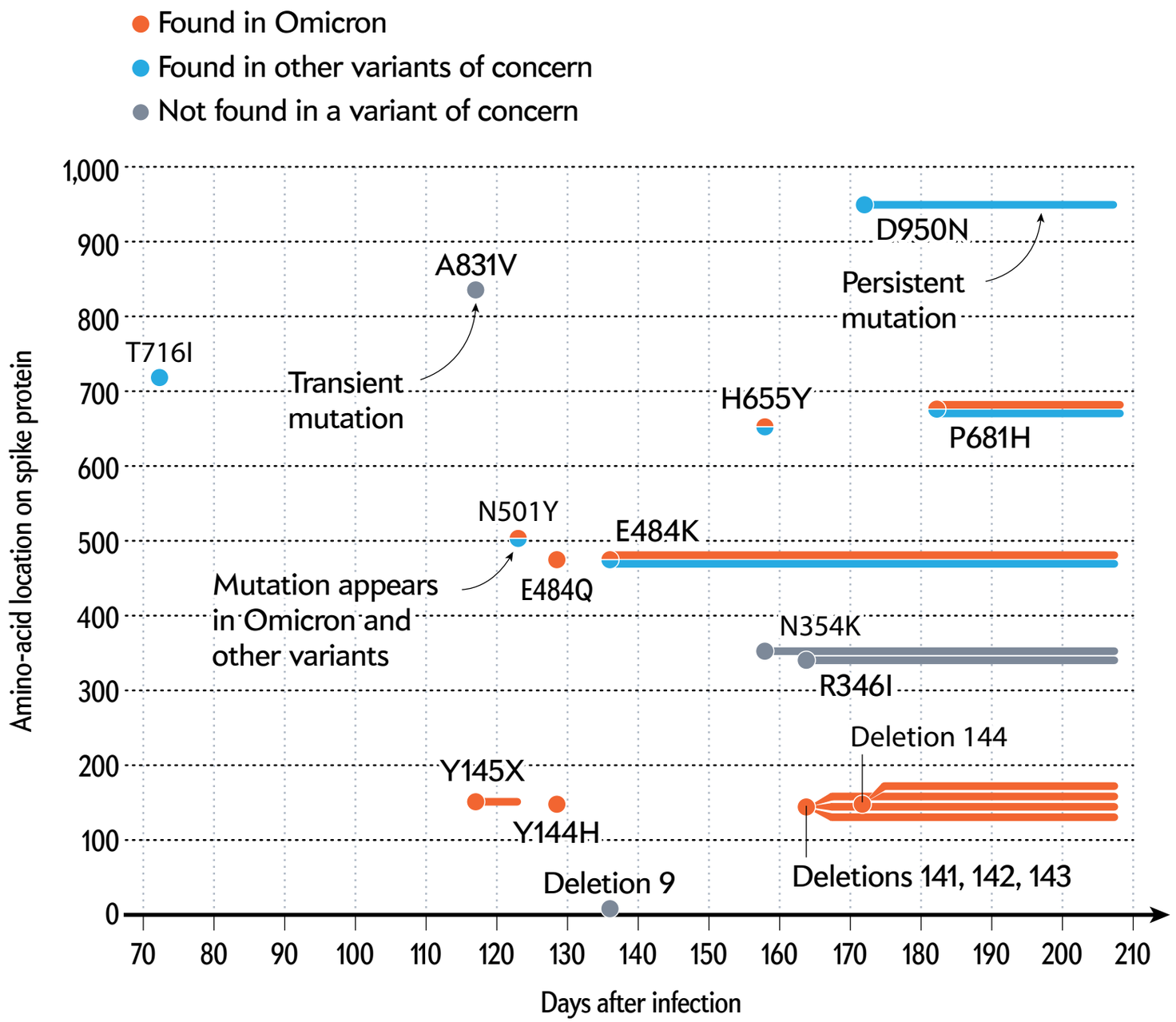
One of the mutations, called D796H, conferred resistance to antibodies—but this benefit came at a cost to the virus. When the researchers engineered a nonreplicating "pseudotype virus" to carry the D796H mutation and measured how well it could infect cells in the lab, they found that this mutation alone made the pseudotype virus significantly less infectious. But when the pseudotype virus also contained a second mutation found in the same person—a two-amino acid deletion at sites 69 and 70—infectivity was restored almost completely. Such compensatory mutations, which have more time to emerge in chronic infections, allow the virus to make evolutionary leaps, Gupta says: "Viruses struggle to do that when they're jumping between hosts very quickly."

In some cases, mutations have made sense only with hindsight. In late 2020 Jonathan Li, a physician-scientist at Brigham and Women's Hospital in Boston, and his colleagues released the first detailed report of a chronic SARS-CoV-2 infection: an ultimately fatal case in a 45-year-old man who had a rare autoimmune disease. The virus developed mutations linked to antibody resistance, including E484K, and another spike mutation called N501Y, which lab studies had suggested improves the virus's ability to bind to host cell receptors, potentially boosting infectivity.

The significance of the N501Y change became apparent when it was detected in a trio of fast-growing lineages later named the Alpha, Beta and Gamma variants of concern (VOCs). Omicron bears this mutation, as well as several others identified in the man's infection. "He really was the harbinger of what was to come," Li says.

Tracking Spike's Evolution

Researchers started sequencing viruses retrieved from a person with chronic COVID-19 on day 73 of the infection. They found eight transient and nine persistent mutations appear in the virus's spike protein before the infection resolved on day 207. Many of these mirror the mutations found in Omicron and other variants of concern.



"How Months-Long COVID Infections Could Seed Dangerous New Variants," by Ewen Callaway, in *Nature*, Vol. 606, June 2022

Isolating people with long-term infections probably won't suppress new variants of concern.

Ina Fassbender/AFP/Getty Images

SEEKING VARIANT ORIGINS

Alpha, identified in the U.K. in late 2020, was the first SARS-CoV-2 variant suspected to have emerged from a chronic infection. But that wasn't the only possible explanation, Rambaut says. The variant might have arisen in a region—probably outside the U.K.—that had little capability to conduct genomic surveillance of SARS-CoV-2. Alternatively, Alpha could have evolved in an animal reservoir (the variant's N501Y mutation enables it to infect mice, rats and mink).

A chance discovery nonetheless suggests that a chronic infection was the most likely source of Alpha. Rambaut and Verity Hill, an evolutionary biologist at the University of Edinburgh, reported in a March preprint the discovery of an intermediate version of Alpha in U.K. sequencing data. The sequence was collected from a person in southeastern England in July 2020, two months before Alpha was first detected in the same region.

The virus had acquired the N501Y mutation, as well as several other hallmarks of Alpha, but it lacked the full suite of changes. "It's accumulating these mutations. It was probably a bit rubbish at spreading," Hill says. Only once the Alpha intermediate gained further mutations did it have the capacity to take off, she suggests.

Combinations of mutations are seen in Omicron, too. That variant—which includes several sublineages with many overlapping mutations—is brimming with genetic changes linked to both immune escape and infectivity that had been spotted before. But what stood out to Martin was that the BA.1 subvariant that set off most countries' Omicron waves has a collection of 13 spike mutations that scientists had rarely seen individually, let alone all together in a single virus.

Martin and his colleagues hypothesize that, among this unique set of mutations, are some that helped to offset the evolutionary costs associated with the mutations that hastened Omicron's spread. "Those trade-offs take a long time to resolve, and those require, in my opinion, chronic infections," Martin says. These could be in humans or in animals, he adds.

Another characteristic of Omicron—the reduced severity of disease—could also be a product of chronic infection. Lab studies have suggested that Omicron's relative mildness could be a result of its preference for infecting cells in the upper airways, as opposed to those in the lung. The variant probably evolved from a strain that adeptly infected both upper and lower airways. Gupta suspects that Omicron's shift probably depended on the kind of coordinated evolution that occurs when a virus spends months in a single person's body. But what's not clear are the evolutionary forces that propelled such a shift, he notes.

ON THE LOOKOUT

Chronic infections could be the best explanation for how variants such as Omicron and Alpha evolved. But it's not obvious how one of the defining characteristics of most variants—their ability to spread like wildfire between people—might evolve in a single individual. "That's a real mystery," Bloom says. "When something's not under selection, you often lose it. During a chronic infection there's no longer selection for transmissibility."

One possible explanation is that the same molecular mechanisms that help SARS-CoV-2 to infect a person's airways, lungs and other organs are also important for enabling the virus to spread to others. "The same transmission dynamics are required when it's inside you as when it's going from one person to another," Martin says.

But there is a difference between a virus that merely retains the ability to transmit and one such as Omicron or Alpha that can cause a global surge in cases. A massive boost in transmissibility or the capacity to infect previously immune people might be what sets a dangerous VOC apart, Rambaut says: "It's not that all chronic infections are going to produce VOCs. It's going to be one in a million."

"We need to go beyond the case reports and understand what the virus is actually evolving during this time."
—Alex Sigal

That means that surveillance is unlikely to detect a variant at its point of emergence. In a May preprint, researchers spotted an Omicron strain that had picked up other spike mutations during chronic infection in an immunocompromised individual and showed that it had spread to several people in the same hospital, as well as in the local community. But wider spread of such infections seems exceedingly rare. A February preprint documenting 27 people with chronic infections reports no evidence that any had spread the virus to other individuals. If VOCs so rarely emerge from chronic infections, it will be difficult to prevent them without reducing overall rates of infection around the world, says Adi Stern, an evolutionary virologist at Tel Aviv University in Israel, who led the study.

Nevertheless, there is an urgent need to understand the viral factors that contribute to chronic infections. "We need to go beyond the case reports and understand what the virus is actually evolving during this time," Sigal says.

Sigal and his team are tracking people with advanced HIV, whose immune systems can be severely compromised, to identify factors associated with chronic SARS-CoV-2 infection. HIV infects immune cells called CD4+ T cells, which also support the production of antibodies against viruses such as SARS-CoV-2. In unpublished work, Sigal and his colleagues have found that low levels of CD4+ T cells are associated with a risk of chronic SARS-CoV-2 infection and that many of the cases are mild, with few or no respiratory symptoms.

On the basis of the sheer number of people living with HIV—nearly 40 million globally—and the likelihood that most people have already been infected with SARS-CoV-2, it seems likely that some cases of persistent infection are contributing to the emergence of new variants, Otto says. "From an Occam's razor point of view, we know that should be a source."

People with compromised immune systems aren't the only potential source of variants. Researchers have documented SARS-CoV-2 infections lasting multiple weeks in people with healthy immune systems. From the perspective of natural selection, even a relatively short three-week infection provides exponentially more opportunities for the virus to evolve, compared with an acute infection lasting a week, Martin says.

People with relatively healthy immune systems might also provide the virus with more selection pressure than individuals who have impaired immune responses, Hill says. But how to identify people who are susceptible to such infections or what their symptoms might look like is an open question. "I would suspect they're a lot more common than we realize," Hill adds.

Last year Gonzalo Bello, a virologist at the Oswaldo Cruz Institute in Rio de Janeiro, and his colleagues identified several strains of SARS-CoV-2 circulating in Amazonas state in Brazil. These carried some—but not all—of the mutations found in the Gamma variant that drove the region's ferocious second wave in 2021. But each of the Gamma-like strains also had their own unique mutations: evidence, Bello says, that Gamma might have

evolved not from a single chronic infection but from transmission chains of medium-length infections involving relatively healthy people.

Such transmission chains could have contributed to the diversity of Omicron lineages, Bello suggests. "Maybe these individuals are where some of the steps in the origin of VOCs are happening," he says. And if chronic infections in healthy people are a likely source of VOCs, improving global vaccination rates could help to prevent new ones emerging, Hill adds: "When you've got these huge uncontrolled waves of infection, you're sowing the seeds for the next."

Antiviral drugs and other treatments taken during a chronic infection could also be playing a part in the virus's evolution. One trait scientists are looking out for is resistance to COVID drugs such as Paxlovid (nirmatrelvir–ritonavir) and molnupiravir. (Resistance to the antiviral remdesivir has already been documented in chronic infections.) The drugs affect highly conserved viral proteins—for which the barrier to drug resistance is high—but evolutionary leaps that characterize chronic infections could buy the virus time to come up with a way around that, Gupta says.

In unpublished laboratory experiments, a team led by virologist David Ho of Columbia University has found that SARS-CoV-2 can take numerous paths to Paxlovid resistance. Some involve gaining compensatory mutations that allow the virus to overcome the costs of Paxlovid resistance, allowing them to thrive, at least in the lab. Such mutations are unlikely to be behind anecdotal reports of recurring SARS-CoV-2 symptoms after Paxlovid treatment, says Ho (who himself experienced such a rebound). But if the treatment, which is normally taken for five days, is administered for a longer period to treat a chronic infection, there is a good chance resistance will emerge.

There is also an urgent need to identify effective treatments for chronic infections—particularly in people with immune system impairments, who don't always mount a strong response to vaccines. Most approved monoclonal antibody drugs are not effective against Omicron and its offshoots, and researchers have shown in a preprint that resistance to these therapies can emerge when they're used to treat chronic infections.

Convalescent plasma should create a higher evolutionary barrier than monoclonal antibody therapies, says Arturo Casadevall, a microbiologist at the John Hopkins Bloomberg School of Public Health. Plasma that contains high levels of diverse antibodies has been shown to be effective at treating COVID, and some physicians are now giving it to people who have compromised immune systems.

Antiretroviral drugs that target HIV can also help people living with that virus to clear chronic SARS-CoV-2 infections, but adherence to the drugs can be a challenge, Sigal notes.

Last October U.K. clinicians reported a case in which a person's chronic infection was cleared after they received a COVID vaccine. For the Austrian woman whom Sonnleitner and her colleagues studied, the end of her seven-month infection also followed vaccination. But it's impossible to know if the vaccine is what helped her to recover.

That outcome is rare for people with chronic infections, however; many reports end in death. "They really are heartbreaking cases," Stern says. As many parts of the world attempt to move on from the pandemic, with some healthy people shrugging their shoulders at mild Omicron infections, Stern says we must do more to protect those who are most at risk of a chronic SARS-CoV-2 infection: "It's dangerous for them—and it's dangerous for us as a society." SA

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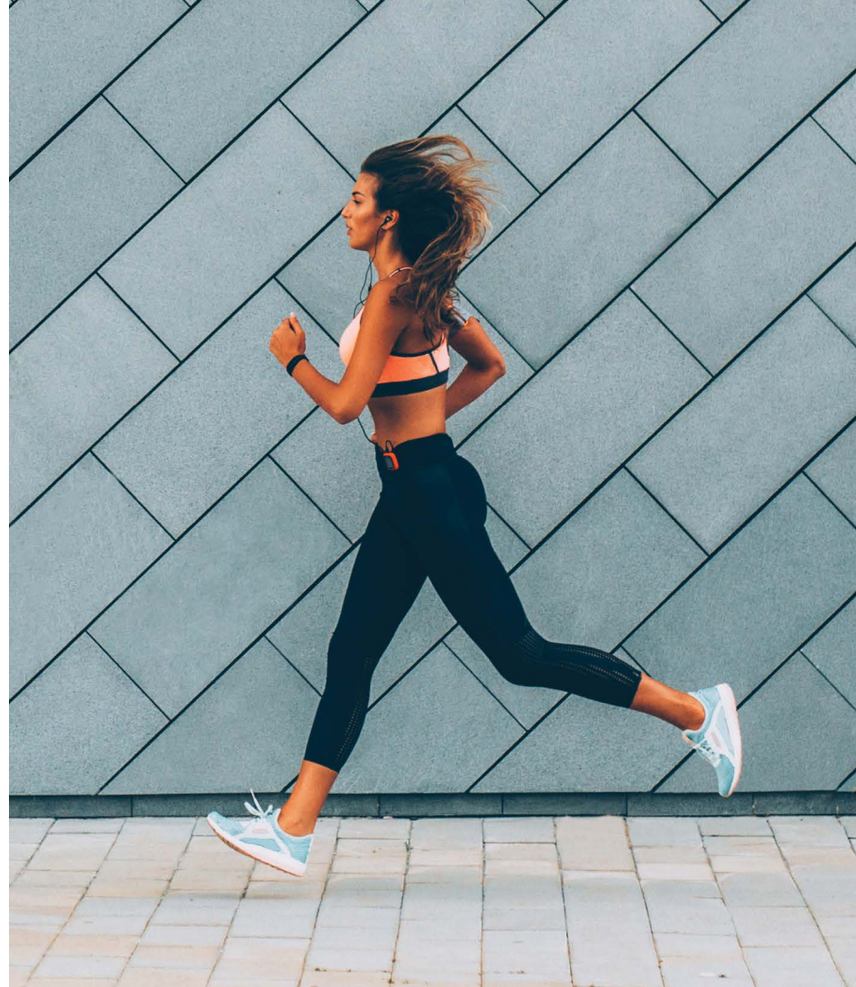

As attacks against transgender kids increase in the U.S., Minnesotans hold a rally at the state's capitol in Saint Paul in March 2022 to support trans kids in Minnesota and Texas and around the country.

What the Science on Gender-Affirming Care for Transgender Kids Really Shows

Laws that ban gender-affirming treatment ignore the wealth of research demonstrating its benefits for trans people's health *By Heather Boerner*

Michael Siluk/UCG/Universal Images Group via Getty Images

Heather Boerner is a health-care and science journalist based in Pittsburgh. Her work has appeared in the *Daily Beast*, the *Washington Post*, the *Atlantic* and *NPR*. Follow her on Twitter @HeatherBoerner

FOR THE FIRST 40 YEARS OF THEIR LIFE, TEXAS RESIDENT KELLY Fleming spent a portion of most years in a deep depression. As an adult, Fleming—who uses they/them pronouns and who asked to use a pseudonym to protect their safety—would shave their face in the shower with the lights off so neither they nor their wife would have to confront the reality of their body.

What Fleming was experiencing, although they did not know it at the time, was gender dysphoria: the acute and chronic distress of living in a body that does not reflect one's gender and the desire to have bodily characteristics of that gender. While in therapy, Fleming discovered research linking access to gender-affirming hormone therapy with reduced depression in transgender people. They started a very low dose of estradiol, and the depression episodes became shorter, less frequent and less intense. Now they look at their body with joy.

So when Fleming sees what authorities in Texas, Alabama, Florida and other states are doing to bar transgender teens and children from receiving gender-affirming medical care, it infuriates them. And they are worried for their children, ages 12 and 14, both of whom are agender—an identity on the transgender spectrum that is neither masculine nor feminine.

"I'm just so excited to see them being able to present themselves in a way that makes them happy," Fleming says. "They are living their best life regardless of what others think, and that's a privilege that I did not get to have as a younger person."

LAWS BASED ON "COMPLETELY WRONG" INFORMATION

Currently more than a dozen state legislatures or administrations are considering—or have already passed—laws banning health care for transgender young people. On April 20 the Florida Department of Health issued guidance to withhold such gender-affirming care. This includes social gender transitioning—acknowledging that a young person is trans, using their correct pronouns and name, and supporting their desire to live publicly as the gender of their experience rather than their sex assigned at birth. This comes nearly two months after Texas Governor Greg Abbott issued an order for the Texas Department of Family and Protective Services to investigate for child abuse parents who allow their transgender preteens and teenagers to receive medical care. Alabama recently passed SB 184, which would make it a felony to provide gender-affirming medical care to transgender minors. In Alabama, a "minor" is defined as anyone 19 or younger.

If such laws go ahead, 58,200 teens in the U.S. could lose access to or never receive gender-affirming care, according to the Williams Institute at the University of California, Los Angeles. A decade of research shows such treatment reduces depression, suicidality and other devastating consequences of trans preteens and teens being forced to undergo puberty in the sex they were assigned at birth.

The truth is that data from more than a dozen studies of more than 30,000 transgender and gender-diverse young people consistently show that access to gender-affirming care is associated with better mental health outcomes—and that lack of access to such care is associated with higher rates of suicidality, depression and self-harming behavior. (Gender diversity refers to the extent to which a person's gendered behaviors, appearance and identities are culturally incongruent with the sex they were assigned at birth. Gender-diverse people can identify along the transgender spectrum, though not all do.) Major medical organizations, including the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry, the Endocrine Society, the American Medical Association, the American Psychological Association and the American Psychiatric Association, have published policy statements and guidelines on how to provide age-appropriate gender-affirming care. All of those medical societies find such care to be evidence-based and medically necessary.

AAP and Endocrine Society guidelines call for developmentally appropriate care, and that means no puberty blockers or hormones until young people are already undergoing puberty for their sex assigned at birth. For one thing, "there are no hormonal differences among prepubertal children," says Joshua Safer, executive director of the Mount Sinai Center for Transgender Medicine and Surgery in New York City and co-author of the Endocrine Society's guidelines. Those guidelines provide the option of gonadotropin-releasing hormone analogues (GnRHas), which block the release of sex hormones, once young people are already into the second of five puberty stages—marked by breast budding and pubic hair. These are offered only if a teen is not ready to make decisions about puberty. Access to gender-affirming hormones and potential access to gender-affirming surgery are available at age 16—and then, in the case of transmasculine youth, only mastectomy, also known as top surgery. The Endocrine Society does not recommend genital surgery for minors.

Before puberty, gender-affirming care is about supporting the process of gender development rather than directing children through a specific course of gender transition or maintenance of cisgender presentation, says Jason Rafferty, co-author of AAP's policy statement on gender-affirming care and a pediatrician and psychiatrist at Hasbro Children's Hospital in Rhode Island. "The current research suggests that, rather than predicting or preventing who a child might become, it's better to value them for who they are now—even at a young age," Rafferty says.

"I'm just so excited to see them being able to present themselves in a way that makes them happy. They are living their best life regardless of what others think, and that's a privilege that I did not get to have as a younger person."
—Kelly Fleming

A SAFE ENVIRONMENT TO EXPLORE GENDER

A 2021 systematic review of 44 peer-reviewed studies found that parent connectedness, measured by a six-question scale asking about such things as how safe young people feel confiding in their guardians or how cared for they feel in the family, is associated with greater resilience among teens and young adults who are transgender or gender-diverse. Rafferty says he sees his role with regard to prepubertal children as offering a safe environment for the child to explore their gender and for parents to ask questions. "The gender-affirming approach is not some railroad of people to hormones and surgery," Safer says. "It is talking and watching and being conservative."

Only once children are older, and if the incongruence between the sex assigned to them at birth and their experienced gender has persisted, does discussion of medical transition occur. First a gender therapist has to diagnose the young person with gender dysphoria.

After a gender dysphoria diagnosis—and only if earlier conversations suggest that hormones are indicated—guidelines call for discussion of fertility, puberty suppression and hormones. Puberty-suppressing medications have been used for decades for cisgender children who start puberty early, but they are not meant to be used indefinitely. The Endocrine Society guidelines recommend a maximum of two years on GnRHa therapy to allow more time for children to form their gender identity before undergoing puberty for their sex assigned at birth, the effects of which are irreversible.

"[Puberty blockers] are part of the process of 'do no harm,' " says Michelle Forcier of Brown University, referencing a popular phrase that describes the Hippocratic Oath, which many physicians recite a version of before they begin to practice.

Hormone blocker treatment may have side effects. A 2015 longitudinal observational cohort study of 34 transgender young people found that, by the time the participants were 22 years old, trans women experienced a decrease in bone mineral density. A 2020 study of puberty suppression in gender-diverse and transgender young people found that those who started puberty blockers in early puberty had lower bone mineral density before the start of treatment than the public at large. This suggests, the authors wrote, that GnRHa use may not be the cause of low bone mineral density for these young people. Instead they found that lack of exercise was a primary factor in low bone-mineral density, especially among trans girls.

Other side effects of GnRHa therapy include weight gain, hot flashes and mood swings. But studies have found that these side effects—and puberty delay itself—are reversible, Safer says.

Gender-affirming hormone therapy often involves taking an androgen blocker (a chemical that blocks the release of testosterone and other androgenic hormones) and estrogen in transfeminine teens and testosterone supplementation in transmasculine teens. Such hormones may be associated with some physiological changes for adult transgender people. For instance, transfemi-

nine people taking estrogen see their so-called good cholesterol increase. In contrast, transmasculine people taking testosterone see their good cholesterol decrease. Some studies have hinted at effects on bone mineral density, but these are complicated and also depend on personal, family history, exercise, and many other factors in addition to hormones."

And while some critics point to a decade-old study and older studies suggesting very few young people persist in transgender identity into late adolescence and adulthood, Forcier says the data are "misleading and not accurate." A recent review detailed methodological problems with some of these studies. New research in 17,151 people who had ever socially transitioned found that 86.9 percent persisted in their gender identity. Of the 2,242 people who reported that they reverted to living as the gender associated with the sex they were assigned at birth, just 15.9 percent said they did so because of internal factors such as questioning their experienced gender but also because of fear, mental health issues and suicide attempts. The rest reported the cause was social, economic and familial stigma and discrimination. A third reported that they ceased living openly as a trans person because doing so was "just too hard for me."

"The gender-affirming approach is not some railroad of people to hormones and surgery. It is talking and watching and being conservative."
—Joshua Safer

THE HARMS OF DENYING CARE

Data suggest the effects of denying that care are worse than whatever side effects result from delaying sex-assigned-at-birth puberty. And medical society guidelines conclude that the benefits of gender-affirming care outweigh the risks. Without gender-affirming hormone therapy, cisgender hormones take over, forcing body changes that can be permanent and distressing.

A 2020 study of 300 gender-incongruent young people found that mental distress—including self-harm, suicidal thoughts and depression—increased as the children were made to proceed with puberty according to their assigned sex. By the time 184 older teens (with a median age of 16) reached the stage in which transgender boys began their periods and grew breasts and transgender girls' voice dropped and facial hair began to appear, 46 percent had been diagnosed with depression, 40 percent had self-harmed, 52 percent had considered suicide, and 17 percent had attempted it—rates significantly higher than those of gender-incongruent children who were a median of 13.9 years old or of cisgender kids their own age.

Conversely, access to gender-affirming hormones in adolescence appears to have a protective effect. In one study, researchers followed 104 teens and young adults for a year and asked them about their depression, anxiety and suicidality at the time they started receiving hormones or puberty blockers and again at the three-month, six-month and one-year mark. At the beginning of the study, which was published in *JAMA Network Open* in February 2022, more than half of the respondents reported moderate to severe depression, half reported moderate to severe anxiety, and 43.3 percent reported thoughts of self-harm or suicide in the past two weeks.

But when the researchers analyzed the results based on the kind of gender-affirming care the teens had received, they found that those who had access to puberty blockers or gender-affirming hormones were 60 percent less likely to experience moderate to severe depression. And those who had access to the medical treatments were 73 percent less likely to contemplate self-harm or suicide.

"Delays in prescribing puberty blockers and hormones may in fact worsen mental health symptoms for trans youth," says Diana Tordoff, an epidemiology graduate student at the University of Washington and co-author of the study.

That effect may be lifelong. A 2022 study of more than 21,000 transgender adults showed that just 41 percent of adults who wanted hormone therapy received it, and just 2.3 percent had access to it in adolescence. When researchers looked at rates of suicidal thinking over the past year in these same adults, they found that access to hormone therapy in early adolescence was associated with a 60 percent reduction in suicidality in the past year and that access in late adolescence was associated with a 50 percent reduction.

For Fleming's kids in Texas, gender-affirming hormones are not currently part of the discussion; not all trans people desire hormones or surgery to feel affirmed in their gender. But Fleming is already looking at jobs in other states to protect their children's access to such care, should they change their mind. "Getting your body closer to the gender [you] identify with—that is what helps the dysphoria," Fleming says. "And not giving people the opportunity to do that, making it harder for them to do that, is what has made the suicide rate among transgender people so high. We just—trans people are just trying to survive."

We Need to Improve Indoor Air Quality: Here's How and Why

Upgrading buildings' ventilation, filtration and other factors would not only decrease COVID transmission but also improve health and cognitive performance in general

By Tanya Lewis

Air-purification device stands in a classroom at an elementary school in Berlin.

Annette Riedl/dpa/Alamy Live News

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WE SPEND 90 PERCENT OF OUR lives indoors, yet most of us seldom spare a thought for the quality of the air we breathe there.

More than a century ago pioneering nurse and statistician Florence Nightingale proclaimed the importance of open air and bedroom ventilation for tuberculosis patients. Today in Nordic countries, it is common practice to let babies nap outside, sometimes in freezing temperatures. But even though humans have long attributed health benefits to fresh outdoor air, it is a lesson many of us seemed to have largely forgotten—until the COVID-19 pandemic forced us to relearn it.

It is now widely acknowledged that SARS-CoV-2, the virus that causes COVID, is frequently transmitted by airborne droplets called aerosols that hang in the air and can travel over short and long distances. "This is a virus that spreads through the air almost exclusively indoors. If we start there, then the building matters," says Joseph Allen, an associate professor at the Harvard T. H. Chan School of Public Health and director of its Healthy Buildings program.

As the U.S. and many other countries drop mask mandates and other short-term measures to help reduce the spread of SARS-CoV-2, improving indoor air quality is becoming even more crucial. "As we start to shift away from these broad government mandates and regulations, we need strategies ... that are passive, that are operating in the background," Allen says. "Clean air shouldn't be partisan."

Cleaner indoor air has other benefits besides reducing COVID risk. Influenza and other respiratory viruses also spread through the air and cause a huge amount of illness and lost productivity. Plus, studies have shown that poor ventilation has all kinds of other health effects, from "sick building syndrome" to cognitive impacts.

Perhaps society could take a lesson from the way it regards water treatment. Extensive measures are taken to ensure water quality in public systems. Why not do the same for air?

For the most part, "we don't rely on people in the U.S. to filter their water individually; we provide clean, safe drinking water," says Linsey Marr, a professor of civil and environmental engineering at Virginia Tech and a leading expert on aerosol transmission of viruses. "I think it's time to start thinking about our indoor air in the same way."

"ACCEPTABLE" AIR QUALITY

In the past 40 years or so, engineers have designed buildings to have tighter "envelopes"—meaning they allow less air exchange with the outside—to improve energy efficiency, according to Allen. But the upshot of this is that many of our buildings are now optimized germ factories.

Much attention is paid to the quality of outdoor air—that is one of the main roles of the U.S. Environmental Protection Agency. But people spend much more time indoors, where we are routinely exposed not just to environmental pollutants but to indoor ones ranging from pathogens to cooking fumes to chemicals released by furniture.

"Humans are incredible indoor creatures," says Richard Corsi, dean of the College of Engineering at the University of California, Davis. The average U.S. lifespan before the pandemic was about 79 years, and "we spend 69 years inside buildings." Of that, Corsi notes, "54 years are spent inside of homes."

The American Society of Heating and Air-Conditioning Engineers (ASHRAE) is a U.S. industry body that sets standards for what it calls "acceptable indoor air quality." For nonresidential buildings, this is defined as "air in which there are no known contaminants at harmful concentrations, as determined by cognizant authorities, and with which a substantial majority (80 percent or more) of the people exposed do not express dissatisfaction." For residential buildings, the definition is "air toward which a substantial majority of occupants express no dissatisfaction with respect to odor and sensory irritation and in which there are not likely to be contaminants at concentrations that are known to pose a health risk."

Allen says building designers and managers should be striving for something better than merely "acceptable." These standards are "well below" what is needed to protect against COVID, influenza and other infectious diseases, he says. Others agree. "Think about if somebody's selling a car and used that kind of advertising: 'Purchase our car; it will be acceptable to you,'" Corsi says. "I don't think a lot of people would buy that car."

ASHRAE standards aim to limit exposure to harmful substances with known exposure limits, such as formaldehyde and other volatile organic compounds, but

CO_2 meters such as this one in a restaurant in Galicia, Spain, can serve as a proxy for the amount of ventilation in a building. Numbers below 800 parts per million indicate a good amount of air exchange.

not to pathogens—for which there are far fewer data—according to William P. Bahnfleth, chair of the ASHRAE Epidemic Task Force and a professor of architectural engineering at Pennsylvania State University. "Current minimum ventilation rates—alone—do not provide complete mitigation of airborne disease transmission risk," Bahnfleth wrote in an e-mail to *Scientific American*. He added that although transmission risk cannot be reduced to zero, combining precautions such as vaccination, mask use and occupancy limits with engineering practices, including ventilation, filtration and air disinfection, "is the most effective way to minimize risk."

Changing air-quality standards takes time. Meanwhile some steps can be taken immediately to improve the air we breathe indoors. These steps involve strengthening four main pillars of indoor air quality: source control, ventilation, filtration and disinfection.

SOURCE CONTROL

In 1858 chemist Max von Pettenkofer, one of the pioneers of the indoor air-quality movement, wrote that if a space contains a pile of manure, one should not try to remove the odor by ventilation but rather remove the manure.

In modern, broader terms, this means that people can prevent pollutants from being released into the air in the first place by limiting potential sources. For example, one could reduce cooking fumes by using an electric stove instead of a gas one.

When it comes to pathogens like SARS-CoV-2, a person who has been knowingly exposed could wear a high-quality mask or could stay home if they have any symptoms.

Of course, such measures alone cannot prevent all pathogens or other pollutants from entering the air, which is why other steps are needed.

VENTILATION

A building's ventilation level refers to how much fresh outdoor air is being brought in; this fresh air dilutes the concentration of virus-laden particles in the air. Imagine a SARS-CoV-2 particle indoors as a drop of food coloring in a cup of water. Outdoors, it is more like a drop of dye in the ocean—it rapidly becomes so diluted as to be undetectable. Ventilation makes the indoor "cup" more like the outdoor "ocean."

The simplest and cheapest way to improve ventilation is to open a window, but that is not always a viable option—especially if the air outside is more polluted than that inside. "This is a huge equity issue. Not everyone can open the windows and bring in fresh air," says Kimberly Prather, an atmospheric chemist and professor at the Scripps Institution of Oceanography and the University of California, San Diego. People of color, for example, are more likely to live and work in places where they are exposed to harmful pollution. Wildfire smoke also frequently creates poor air quality in many parts of the western U.S.

M. Dylan/Europa Press via Getty Images

Aside from windows, another source of indoor airflow is a heating, ventilation and air conditioning (HVAC) system. Most of these systems allow a building manager to vary the amount of fresh air intake. It should generally be set to maximum, experts say—provided the outdoor air quality is safe. Yet many buildings, especially before the pandemic, have had their HVAC system set to recirculate old, stale air. A good rule of thumb is to aim for having at least six air exchanges per hour through ventilation or the equivalent amount of fresh air through filtration.

One way to assess the amount of ventilation in a space is to use a carbon dioxide monitor. Humans exhale CO_2 when we breathe, so levels of this gas provide a good proxy for how diluted the air is. Values below about 800 parts per million are potentially well ventilated, according to the U.S. Centers for Disease Control and Prevention.

FILTRATION

Filtration involves removing particles and other pollutants from the air. A standard called minimum efficiency reporting values (MERV) offers a way of comparing different filters. The gold standard filter is a high-efficiency particulate air (HEPA) filter, which can remove 99.97 percent of airborne particles that are 0.3 micron in size, and an even greater percentage of larger or smaller particles (both of which are trapped more efficiently). HEPA is equivalent to a rating of MERV 17 or higher. Prather and Corsi both recommend upgrading filters to at least MERV 13 for most indoor settings such as schools or offices. Many HVAC systems can be upgraded to this standard—but some very old ones may have trouble with higher-efficiency filters, and this could cause air to leak around the filters, so it's a good idea to check with an HVAC expert.

If the building in question does not have an HVAC system—many homes, for example, do not—one option is to purchase one or more portable air cleaners. These devices generally work well, provided they are the appropriate size for a room. They can be run at high speed to filter the air more quickly during specific times such as a party or when someone in the family is sick with COVID.

"It's a massive win to have the White House signal that healthy buildings are one of the pillars of pandemic response."
—Joseph Allen

Portable air cleaners are not cheap, however; a good-quality model starts at around $200, and the price goes up from there. Fortunately, some researchers have come up with a more affordable solution known as a Corsi-Rosenthal box. Named after U.C. Davis's Corsi and Jim Rosenthal, CEO of filter manufacturer Tex-Air Filters, who both helped develop the idea, it is basically a DIY air cleaner made up of a box fan and four or five MERV filters duct-taped together. Instructions for building these boxes are available online, and they work surprisingly well. A Corsi-Rosenthal box in a 200-square-foot (about 19-square-meter) dorm room achieved the equivalent of about 24 air exchanges per hour—on par with a typical U.S. hospital and better than most similarly sized portable air cleaners. This is because, even though a Corsi-Rosenthal box's filtration efficiency is lower than that of the HEPA filters in most portable air cleaners, the flow rate is much greater, thanks to the large fan. The only complaint is the noise, but Corsi and his colleagues are working on quieter designs.

AIR DISINFECTION

Finally, there is air disinfection: inactivating viruses using ultraviolet light. This is best for high-risk environments such as hospitals or school cafeterias, Virginia Tech's Marr says. It works by shining UV light across the top of a room, which neutralizes airborne pathogens as they circulate through that space. Some wavelengths of UV light are harmful to humans, although there is a wavelength called far UVC that may be safer for people.

Most UV systems are expensive to install, however. And there's a lot of snake oil out there. "If it sounds too good to be true," Marr says, "it probably is." For most homes and small businesses, focusing on ventilation and filtration is probably the easiest way to improve air quality.

INVESTING IN BETTER AIR

The Biden administration recently called on building managers in schools, universities and other settings to improve indoor air quality and also held a public briefing to draw attention to the importance of clean indoor air. Upgrading air quality can be expensive, but there are federal funds to support such efforts. According to a White House statement, the American Rescue Plan contains $122 billion to help schools stay open and $350 billion for state, local and tribal governments to upgrade ventilation and other infrastructure in local establishments and businesses.

"It's a massive win to have the White House signal that healthy buildings are one of the pillars of pandemic response," Harvard's Allen says.

COVID has injected momentum into efforts to improve air quality inside buildings, and experts hope this momentum will result in lasting investments in this area.

"I think we are on the cusp of a new awareness about indoor air quality," Marr says. "It's so bad in many places that there's lots of room for improvement." Upgrading buildings will require an investment, Marr adds, but one that "I believe will pay off in terms of improved health and productivity."

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Pediatric Gun Deaths Are a Massive Problem in the U.S.

Thoughts and prayers do not stop bullets. We must do better for our children

March for Our Lives demonstration protested gun violence in Washington, D.C., in March 2018.

Rob Crandall/Alamy Stock Photo

School shootings feel random in their location yet predictable in their occurrence. Killers target elementary, high school and college students in urban, suburban and rural communities. The children killed are Hispanic, white, Black, Asian, Native American, gay, straight, transgender and cisgender.

This year school shootings have occurred more than weekly on average, with 27 in 2022 (so far). Many go virtually unmentioned on the national stage, however, until the "unthinkable" happens, and 19 nine- to 11-year-old children and two teachers die unspeakable deaths at Robb Elementary School in Uvalde, Tex. Yet these killings aren't unthinkable. We've been here before—at Columbine, Sandy Hook, Marjory Stoneman Douglas High School in Parkland, Fla., and too many other schools.

We are researchers and pediatric emergency medicine physicians who study firearm injuries. After many hard, politically fraught years of investigating this subject, we believe that it is our collective responsibility to address, head on, the interlinked issues of gun availability, gun safety, gun regulations and gun violence prevention research—and, dare we say it, the politicization of guns taking priority over public health. With thousands of children killed every year in the U.S. by firearms, we must, as a country, ultimately reckon with the essential question of what is most important: Is it the narrow focus on individuals' rights or the broader vision of societal responsibility?

Are pediatric gun deaths really a problem in the U.S.? Our work and others' show the answer is unequivocally yes. Guns kill more U.S. children and adolescents between one and 19 years old than any other means. Guns kill more children than motor vehicle collisions, cancer, infections or any

other disease. And this is a uniquely American problem. Though horrifying and sensational, school deaths represent only a small fraction firearm deaths. Most firearm injuries and deaths happen in homes or neighborhoods. In 2020, 10,197 children and young adults age zero to 24 year old died by guns, a 55 percent increase over the decade prior.

Gun deaths are also a health disparity issue. Over the past decade, a 55 percent increase over the decade prior. Gun deaths are also a health disparity issue. Over the past decade Black teenage boys died by guns at rates about five times higher than those of white teenage boys, although their names rarely register in the national consciousness.

There are at least 400 million guns in the U.S. We don't really know how many because most states don't track gun sales or require gun registration, thanks to successful lobbying by the gun industry and progun politicians. Last year 18.9 million guns were sold in the U.S. And between the beginning of 2019 and middle of 2021, an estimated 7.5 million people became first-time gun owners. This includes 5.4 million people who previously lived in homes without guns. Twenty years ago a majority of gun owners used guns for hunting and sports. Today 88 percent of them state they own their guns for self-protection. Most of those owners say having a gun at home makes them feel safer, and about 40 percent keep one loaded and "easily accessible" at all times. In 2021 four in 10 children, representing approximately 30 million kids, had at least one gun in the home. Even in homes with children, 73 percent of these guns were stored unlocked and/or loaded, putting those children at risk of injury and death. If you keep a gun in your home, storing it unloaded and keeping the gun and ammunition locked away separately can decrease the risk.

Unlike cars and virtually every product sold in the U.S., there are no regulatory safety requirements for guns. That bears repeating: guns are exempt from safety standards set by the federal Consumer Product Safety Act. Between 2015 and 2021, there were 2,446 unintentional child shootings, resulting in 923 deaths and 1,603 injuries. Thus, while pill bottle makers, hair dryer producers and motor vehicle companies constantly work to improve their products' safety, the U.S. government has decreed gun manufacturers do not need to consider whether a two-year-old should be able to pull the trigger on a gun or whether a teenager should be able to fire a gun they don't own.

Beyond these lack of safety requirements, in 2006 Congress passed the Protection of Lawful Commerce in Arms Act,, which shields firearm manufacturers against liability for any injuries or deaths from guns. Thus, gunmakers have minimal incentive to improve gun safety technology, despite the development of safer gun technology over the past decade in the form of personalized "smart" guns, which use fingerprint technology , which use fingerprint technology such as your cell phone, radio-frequency identification (RFID) or other methods to allow only the authorized user to fire the gun. This simple fix would prevent curious children, suicidal individuals and unauthorized people from finding a gun and shooting the weapon. It would save countless lives every year.

We know that states with stronger firearm laws are associated with lower firearm deaths. We also know no one law or strategy will address the problem of U.S. gun violence. We need a multi-pronged strategy, and we need it to encompass all states.

One approach would treat owning guns like owning cars: meaningful age limits for purchase and possession and licensing, registration and insurance requirements. Some states, including New York, Connecticut and California, do have meaningful age limits and licensing and registration requirements. Other states, including Florida, Georgia, Tennessee and Rhode Island, specifically prohibit gun registries. Nearly two thirds of Americans, including 53 percent of Republicans, support moderate or strong regulation of gun ownership. And after every school shooting, federal firearm legislation, such as universal background checks or raising the legal age to buy a long gun from 18 to 21, is proposed once again. It is the most practical start to decreasing firearm deaths yet the most quickly dismissed. So we are left with "thoughts and prayers."

We also need laws to minimize access to firearms among individuals at risk of harming themselves or others (such as people who have been charged with domestic violence or who have homicidal ideation). These needed measures include universal background checks (supported by 81 percent of Americans) and extreme risk protection order ("red flag") laws that allow a judge to prohibit at-risk individuals' purchase or possession

of a firearm for a time limited period. Nineteen states plus Washington, D.C., have red flag laws. These laws are frequently passed by bipartisan consensus in Republican-led states. Yet people slip through the cracks, so we need to both increase awareness of the laws in the states that have them and to have more states pass them.

As pediatric emergency physicians, we specifically concern ourselves with children accessing their parents' guns. Strong child access prevention laws, currently in 34 states and Washington, D.C., hold adult gun owners liable if a child can or does access a firearm. But we and others have concerns about criminalizing grieving families and nondiscriminatory applications of these laws. Another approach would be to incentivize gun owners to store their firearms more safely.

And then there is funding. Because of a dearth of federal research funding, there are substantial gaps in knowledge about the victims and perpetrators of gun violence, as well as effective interventions. There was no congressional federal funding for firearm research at the Centers for Disease Control and Prevention after Congress passed the Dickey Amendment in 1996—and no such funding for the National Institutes of Health after the amendment was extended to that agency in late 2011—until 2019, when $25 million was appropriated. This is a drop in the bucket, compared with the number of people affected by gun violence. In contrast, the National Heart, Lung, and Blood Institute has a budget of $3.8 billion to support research related to conditions such as heart disease and cancer.

But while we consider these approaches, we must remember these names. They are sons and daughters, children whose parents had hopes and dreams for them, youth with goals and aspirations for themselves:

Nevaeh Bravo
Jacklyn "Jackie" Cazares
Makenna Lee Elrod
Jose Flores, Jr.
Eliana "Ellie" Garcia
Irma Garcia
Uziyah Garcia
Amerie Jo Garza
Xavier Lopez
Jayce Luevanos
Tess Marie Mata
Maranda Mathis
Eva Mireles
Alithia Ramirez
Annabell Guadalupe Rodriguez
Maite Yuleana Rodriguez
Alexandria "Lexi" Aniyah Rubio
Layla Salazar
Jailah Nicole Silguero
Eliahana Cruz Torres
Rojelio Torres

And never again should we have to list the names of innocent children shot and killed in their elementary school. Yet history, and a contemptuous lack of action from our elected officials, predicts we will. We must demand more, especially when there are actions we can take. We must do better for our children, our youth and our society. We must.

Adebayo Adesomo is a fellow in the department of maternal-fetal medicine and instructor in the department of obstetrics and gynecology at the University of Utah. His M.D. is from the University of Texas Health Science Center.

Pregnancy Is Far More Dangerous Than Abortion

Restricting access to and prohibiting abortion in the U.S. will only increase maternal mortality in the nation that already ranks shockingly low in maternal health

MBI/Alamy Stock Photo

In my medical practice, where I treat people with high-risk pregnancies, I recently treated a young woman with pulmonary hypertension. Unfortunately, this diagnosis was made late into her second trimester, well after most states allow pregnancy termination. We had to have the difficult conversation that, despite all modern medical advances, as many as one in three women with this condition will die during pregnancy. Based on that information, who should decide what level of pregnancy risk is acceptable for her? Should she? Should her government? Her case illustrates some of what's at stake, especially now that the U.S. Supreme Court has overturned *Roe v. Wade*.

The risk any person accepts in continuing a pregnancy to term exceeds that of an early safe abortion by literally an order of magnitude. If women such as my patient have no other option than to carry a pregnancy to term, the U.S., which already ranks last out of all developed nations in maternal health, will only deepen its ongoing maternal mortality crisis.

Forcing people to undertake these risks against their will is a fundamental violation of bodily autonomy and human rights, yet multiple states stand poised to ban almost all abortions given that the court has revoked this right to terminate a pregancy. As noted in a recent editorial in the *Lancet,* a leading medical journal, the Supreme Court justices and their supporters who seek to abolish abortion will have "blood on their hands."

Current maternal mortality statistics from the CDC paint a sobering picture. In 2019, 754 mothers died during pregnancy. In 2020, another 850 patients died because of pregnancy-related events. For each of those women who died, 70 more suffered a serious maternal morbidity event, defined as a pregnancy-related event requiring a lifesaving intervention or procedure (such as blood transfusion, surgery or admission to the intensive care unit).

And maternal mortality is inextricably bound with race, class and age. Women 45 years or older experienced nearly 10 times the odds of dying from pregnancy as compared with those younger than 35. Black women are three times more likely to die of pregnancy-related causes than white women. As illustrated by my patient with pulmonary hypertension, underlying medical conditions also play a role in pregnancy-related risk—and their prevalence is positively associated with lower socioeconomic status. The systemic inequities that contribute to these outcomes will further exacerbate these disparities in a post-*Roe* America. In a research letter published last year, sociologist Amanda Stevenson estimated that Black women could experience a 33 percent increase in maternal deaths after a total ban on abortions, the most of any demographic group.

Although pregnancy is not a disease, even one that is otherwise uncomplicated can go unexpectedly awry. The changes that the body undergoes during pregnancy that are needed to support an ongoing gestation are still physiologically akin to running a marathon. All of an expecting mother's organs and bodily systems are put to a nine-month endurance test. The work of the heart and lungs increases by 30 to 50 percent (or even more in a twin pregnancy), the kidneys filter more blood, the immune system adjusts, metabolic demands increase substantially, and myriad other changes occur. The way any given individual's body reacts to these changes is unpredictable.

The controversy surrounding pregnancy termination is exceptional in its treatment of abortion as anything but a medical procedure. By juxtaposing the risks of pregnancy against the safety of abortion, the scientific backwardness of limiting access to abortion care is exposed. Allowing states to ban abortions creates many more questions than it answers: Will women with health conditions be able to exercise their reproductive health rights to protect themselves from harm? How will the treatment of other obstetric conditions such as incomplete abortions or ectopic pregnancies be affected? Lives will hang in the balance as states navigate these issues.

Even a seemingly "safe" pregnancy is not without significant risk. The decision of whether to face pregnancy's risks of complications and death should be left to the pregnant person alone. Not to their congressperson. Not to their governor. Not even to their family or physician, who can nonetheless provide support and information. The surest path to having healthy babies is ensuring healthy and willing mothers. We must fight to keep the rights to pregnancy-related decisions solely among those who bear the consequences.

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Antifatness in the Surgical Setting

Weight bias compounds health problems, and surgeons need to recognize and stop it

It was 6:30 A.M., and I was getting ready to head down to the operating room (OR) for the first case of the day: an abdominal wall hernia repair. In preparation for the case, I logged on to the electronic health record portal and read through the patient's medical history and the preoperative notes written by the surgical team. In many of the physician notes, the first line noted the patient's body mass index (BMI) of 41. The patient's ventral hernia was estimated to be 30 by 20 centimeters, one of the largest hernias ever repaired by the surgeon I was working with. The CT scan showed sections of the large intestine protruding through the hernia, which posed a high risk for bowel twisting, which can lead to perforation and sepsis or tissue deoxygenation and necrosis. The patient's condition had reached a critical point.

I ventured down to the OR and located the CT and MRI images, as part of my medical student role of assisting the nursing and scrub technicians in prepping the OR prior to surgery. I projected the scans onto the large screen TVs hanging in the OR to help the surgeons better visualize the anatomy and their approach. As I pulled up the images, the team in the room erupted in shock. How could someone let a hernia get this bad before seeking medical consultation, they wondered. And others couldn't believe that someone could live with such a large defect and not want it fixed for cosmetic purposes. After rolling the patient into the OR and moving her onto the operating table, the team began to prep the surgical site. As she drifted off into a state of sedation, medical staff in the room could not stop talking about her BMI. The comments were unrelenting throughout the five-hour procedure, as people took turns gawking at the gaping hole in the patient's abdomen. Two of the largest pieces of Strattice biologic mesh made by the supplier were sewn together to repair the hernia. The estimated cost of the mesh alone was $30,000.

As the surgery ended, I couldn't stop thinking about the obvious, yet ironic, connection between the weight comments from the health-care team and why the patient procrastinated before getting

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the surgery. Why would anyone want to interact with a medical system that looked at them in such a derogatory way?

Antifatness is socially ingrained and virtually inescapable. Pop culture idolizes thinness. The Centers for Disease Control and Prevention created an alarmist "obesity epidemic" based on exaggerated data that haven't held up. Like everyone else in society who is socially conditioned to this bias, clinicians are not exempt from harboring antifatness. In a recent study, 24 percent of physicians stated they were uncomfortable having friends in larger bodies, and 18 percent admitted they felt disgusted when treating a patient with a high BMI. This is upsetting yet unsurprising considering that few programs actively train health-care providers against this cognitive bias.

Abundant research demonstrates that "obesity" is not really a choice and is often a product of systemic inequity. The crux of this research explores the multiple systems that underpin weight: food insecurity, housing insecurity, poverty-induced scarcity mindset, medications, diseases, lack of education, mental health issues and chronic stress among them.

Many researchers and scholars have exposed the pervasiveness of antifatness culture, but some of the most prominent actors in maintaining this culture have not been discussed. Surgeons are central to dismantling the problems of antifat bias in health care, and that requires addressing aspects of surgeons' training and day-to-day tasks that may make them more prone to this cognitive bias.

Weight bias is heightened and reinforced in the surgical setting, where surgeries on higher BMI individuals take more time, cost more money and have an increased risk of complications. Antifatness attitudes and behaviors may be higher among surgeons partly as a result of the lack of filter people may have when the patient is sedated. The increased time and care required in these cases can be difficult for surgeons, whose time and care are already strained given staff shortages. Together these factors may lead surgeons to express their frustration through comments about the patient's body.

In addition, professional culture and training are different for surgeons. Primary care physicians' training may focus more on upstream factors contributing to care, including being taught about social determinants of health and multifactorial causes of the patients' conditions. In contrast, surgeons—who on average spend 3,963 hours of training honing a complex motor and visuospatial skill may naturally focus more on the procedural task at hand rather than the factors contributing to their patient's condition. Ultimately a complex motor and visuospatial skill may naturally focus more on the procedural task at hand rather than the factors contributing to their patient's condition. Ultimately the everyday demands of a surgeon's job may make them less likely to think critically about antifatness when providing their day-to-day care. Yet to provide optimal patient care, it is equally important for surgeons to work against weight stigma.

Surgeons are often the physicians who spend the most time in the hospital. As such, they play a vital role in forming the culture in the OR and hospital at large, and their understanding of weight bias and its associated behaviors is critical to counteracting pervasive weight stigma among health-care providers. Postsurgery, many higher-weight patients will require intensive care, continual follow-up and long-term treatment adherence. Patients with a higher weight are also 12 times more likely to have a complication requiring extended hospitalization and continued interface with their surgical team. Surgeons must confront their own weight bias to build positive ongoing partnerships with patients.

A culture of antifatness among surgeons leads to compounding negative impacts on individual patients and the health system. Studies show weight bias from providers is palpable for patients. Patients can sense the lack of dignity and respect in providers' attitudes and, in turn, may choose not to interact with the system that degrades them. Many clinicians turn weight loss into an ultimatum for patients rather than focusing on building their trust, understanding contributing factors and partnering with them to make incremental lifestyle modifications possible. Altogether this can harm patients' self-worth and rapport with providers.

When providers alienate patients who first touch the health-care system, through poor care or rapport, these patients are more likely to not resurface until reaching a critical health point, as with the hernia repair case discussed here. Research suggests that providers spend less time with larger patients, provide a lower quality of care and misdiagnose larger patients more frequently.

Antifatness is often a more socially acceptable

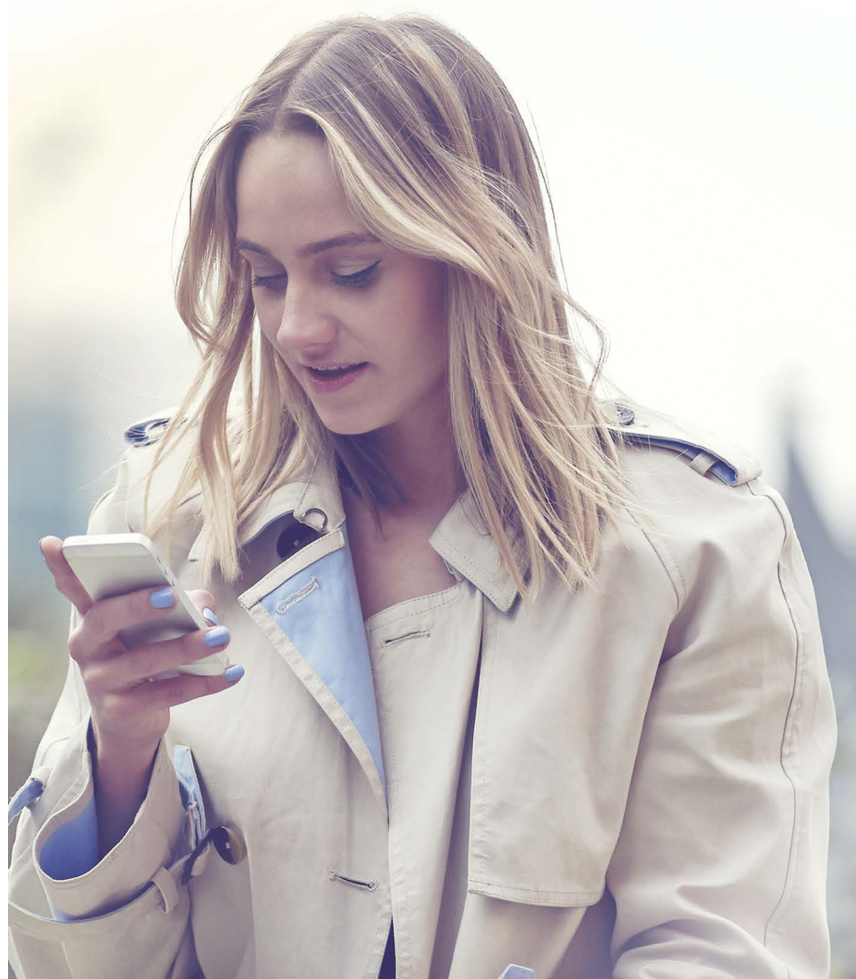
masquerade for anti-Blackness. The Department of Health and Human Services reports that about four out of five African American women are overweight or obese, and Black Americans were 1.3 times more likely to be obese compared with white Americans. This intersection allows covert ways to harm Black and brown bodies.

Ultimately the biases and behaviors that maintain antifatness need to change. Potential avenues for change include creating systemwide education, amending medical documentation, reframing patient conversations and advocating for upstream policies that increase access. A health provider's goal should be health—vital statistics, lab results, symptom reduction, time spent exercising, mental health—not thinness. There are health consequences to obesity, but the current BMI-focused approach is not the best way to capture a person's current health status. Lack of education among medical professionals is perpetuating antifatness. A health systemwide training should be developed to educate health-care providers and shift conscious and unconscious attitudes.

Providers should also make a habit of noting diet and exercise in social history, as opposed to collapsing these factors into BMI. They could partner with patients and connect them with community resources to enable them to meet their health goals of lower blood pressure or better cardiovascular health. Providers can also focus on evidence-based methods, such as educating patients about nutrition, increasing access to food or exercise, discussing weight-loss surgery or medication and employing motivational interviewing. Understanding the multifactorial nature of weight and taking a patient-centered approach early on can ensure patients feel supported and empowered to achieve optimal health outcomes. This affirmative type of partnership will encourage patients to return to the health-care system and invest in the provider-patient relationship and health goals.

Providers must internalize the complexity of weight, learn how to utilize alternative health markers and even advocate for policies that reduce food deserts. Surgeons may read these action items and write them off as tasks reserved for primary care physicians. But practicing unbiased medicine is possible. In one promising model, hospitals in Canada have recently launched a surgical prehabilitation program and toolkit that helps surgeons and their patients work on hypertension, hyperglycemia, hyperlipidemia and cardiovascular health.

Recent movements around self-love and body acceptance are important, but they cannot replace the work that needs to be done by the people who manifest antifatness bias. America does not have an obesity epidemic; it has an unhealthiness epidemic. Yet the worse health outcomes compared to countries with similar economies are just as much a product of antifatness as they are of fatness. Through shame and blame, antifatness may be contributing to obesity and exacerbating poor health. Until surgeons and other health-care providers choose to be a part of the solution to antifatness, then they will be part of the problem.



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