December 2021–January 2022

SCIENTIFIC AMERICAN

Health & Medicine

Kids vs. COVID

Children have fared better with the virus than adults. Immunologists are still trying to figure out why

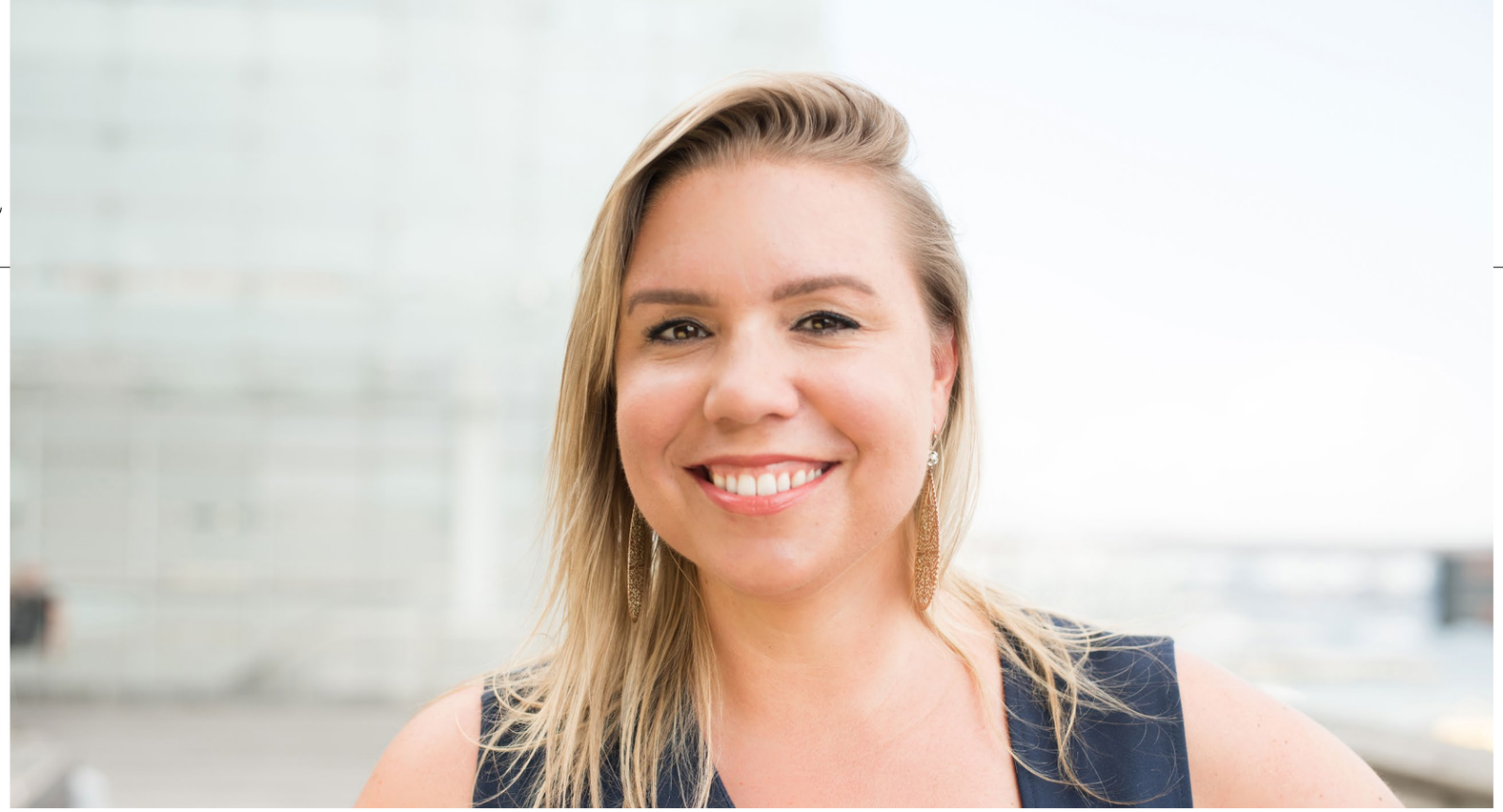
Plus:

THE ONLY MASKS WE SHOULD BE WEARING

NEW FOOD LABELS FOCUS ON HEALTH

HEALING POWERS OF MUSIC

WITH COVERAGE FROM nature



Liz Tormes

Essential Links in the Immunity Web

Beginning in about January of this year, when the first COVID-19 vaccines started becoming available to essential workers and then, within the next few months, to most all adults, friends of mine with young children started asking me: “When will my kids be able to get it?” As the months rolled on, I tried to give them the best guess I could, based on our latest reporting, and by picking my colleagues’ brains at *Scientific American* and other publications. Keeping schools closed for fear of mass outbreaks of the virus was also keeping parents at home and also worrying parents who, despite being vaccinated themselves, didn’t want to unwittingly give the virus to their children.

Finally, in early November, the CDC authorized a pediatric vaccine for kids ages five to 11. It seems a major step toward ending the pandemic and resuming a new normal kind of life. To be sure, the pediatric vaccine protects kids, but it will also lower transmission rates of the virus to any adults the children are in contact with. And perhaps that is the most vital side effect of a new wave of immunizations. As Smriti Mallapaty writes in this issue, children have always shown stronger immunity again SARS-CoV-2, for reasons that researchers are still parsing (see “Why Kids Beat Back COVID Better Than Adults”). But by vaccinating the nearly 30 million youngsters who are now eligible, we are lowering the chance that they’ll be potential vectors for the virus and pass it to adults and vulnerable people. If the endgame is to destroy the web of coronavirus transmission, this is a big win.

Andrea Gawrylewski
Collections Editor
editors@sciam.com

Health & Medicine

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Chris Gash

On the Cover

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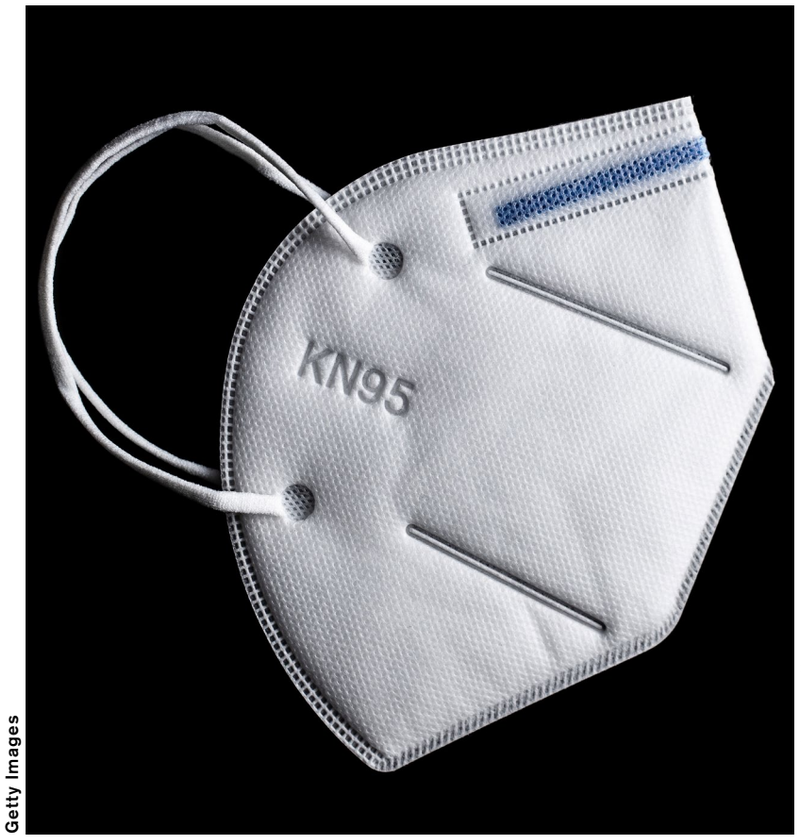

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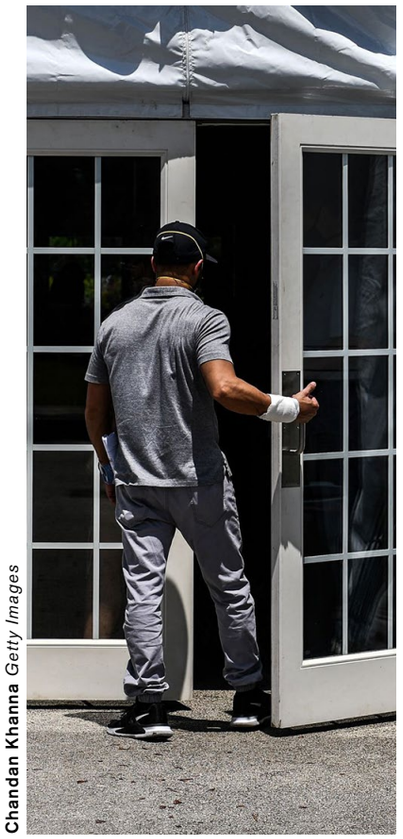

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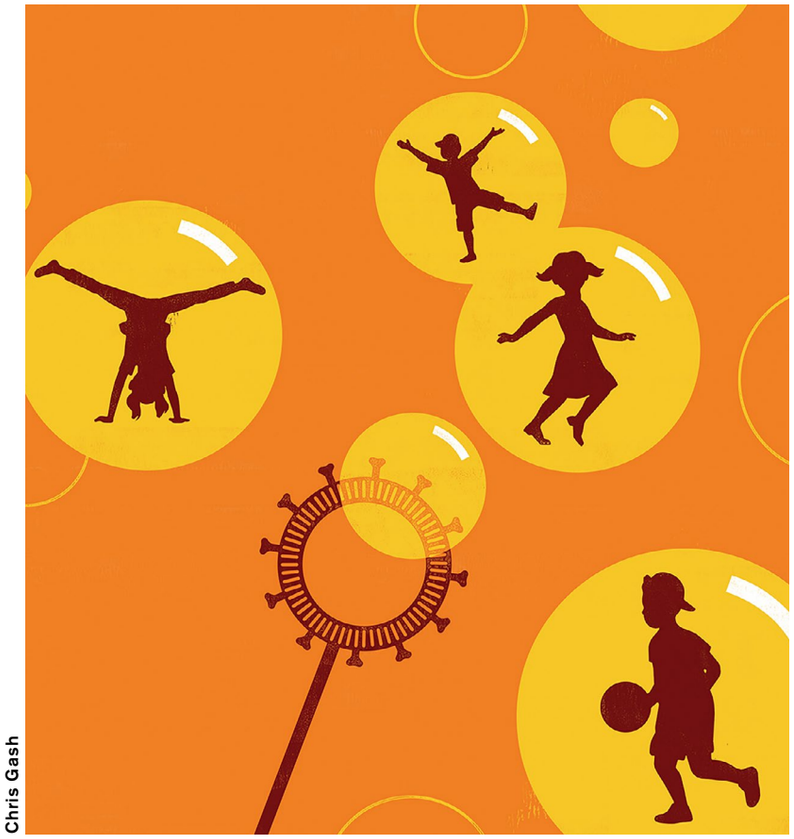


Chris Gash

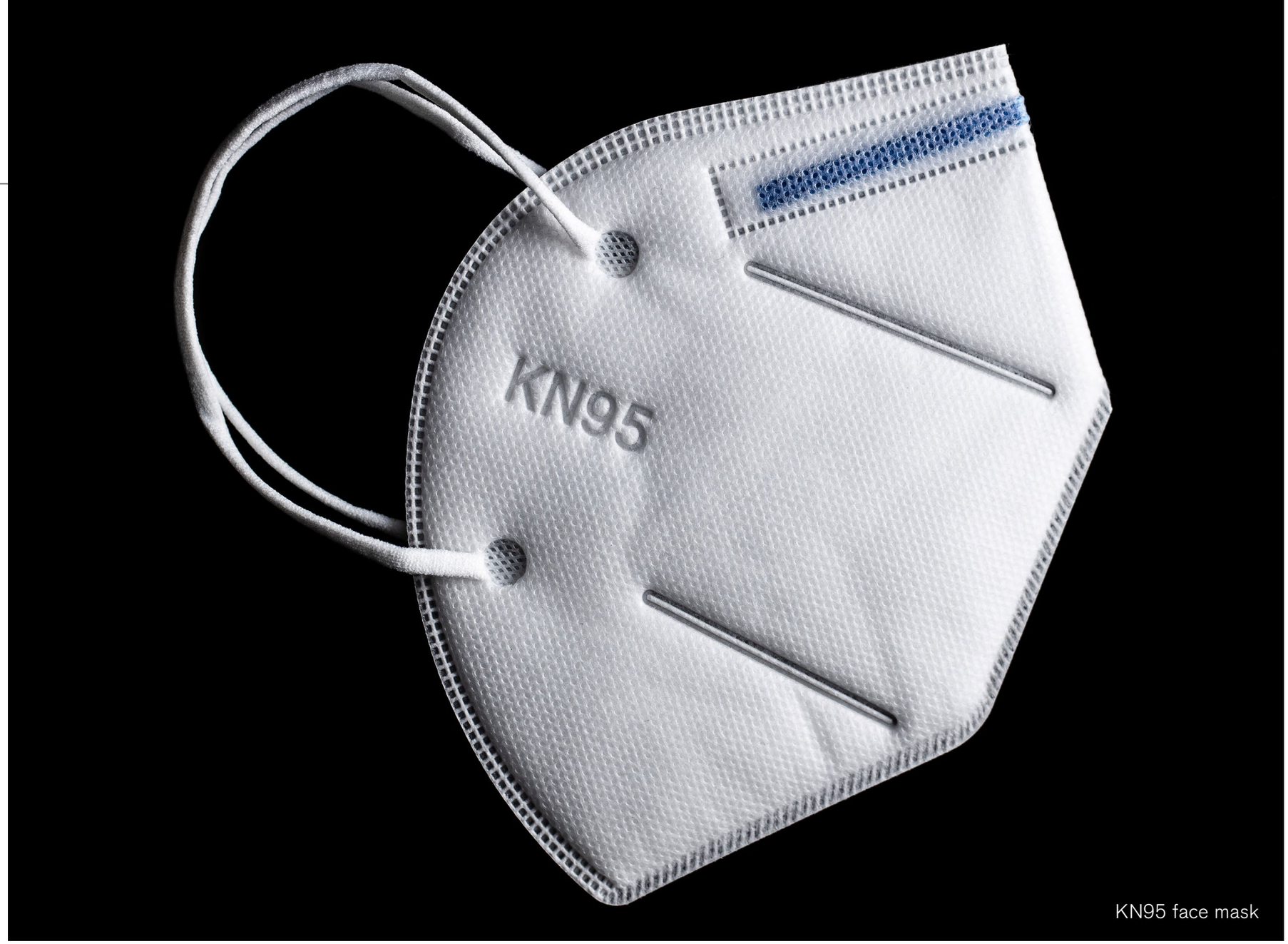
NEWS

FEATURES

OPINION

Why We Need to Upgrade Our Face Masks–and Where to Get Them

High-quality respirators such as N95s and K95s are now widely available and provide the best protection against COVID, according to experts. Why aren't more people wearing them?



KN95 face mask

Getty Images

A wealth of evidence has shown that wearing a face mask helps prevent people from spreading the virus that causes COVID, SARS-CoV-2, to others and from becoming sick themselves. But there has been less guidance from public health officials on what kind of masks provide the best protection.

Early on in the pandemic, the U.S. Centers for Disease Control and Prevention and the World Health Organization told the public not to wear N95 respirators, a type of mask that is made from high-tech synthetic fibers and provides a high level of protection against virus-laden airborne particles called aerosols. That was because there was then a shortage of such masks—and health care workers desperately needed them. At the same time, both agencies said there was little risk of aerosol transmission of SARS-CoV-2. They recommended cloth masks or other homemade face coverings that can stop some relatively large virus-carrying droplets even as it became clear that SARS-CoV-2 commonly spreads through aerosols—and as the supply of better-quality masks increased.

There is now a cornucopia of high-filtration respirator-style masks on the market, including N95s, Chinese-made KN95s and South Korean–made KF94s. They have been widely available and relatively affordable for months and provide better protection than cloth or surgical masks. Yet it was not until September 10 that the CDC finally updated its guidance to say the general public could wear N95s and

other medical-grade masks now that they are in sufficient supply.

Still, however, the "CDC continues to recommend that N95 respirators should be prioritized for protection against COVID-19 in health-care settings," wrote CDC spokesperson Jade Fulce in an e-mail to *Scientific American* in September. "Essential workers and workers who routinely wore respirators before the pandemic should continue wearing N95 respirators," she continued. "As N95s become more available, they can be worn in non-health-care settings; however, cloth masks are an acceptable and recommended option for masking."

The agency announced in May that supplies of approved respirator masks had "increased significantly." When asked why it only updated it guidance on N95 use by the public in September, Fulce replied that the "CDC regularly reviews and updates its guidance as more information becomes available."

Scientific American spoke with several experts on aerosol transmission—some of whom have tested various masks available on the market—and they agree that health authorities should strongly recommend people wear well-fitted, high-filtration masks.

"A year ago we could say that we were concerned about shortages for health-care workers, so we were telling people to make your cloth mask, and any mask is better than no mask," says Linsey Marr, an environmental engineer and aerosol science expert at Virginia Tech. But given what scientists know now—especially with the virus's highly transmissible Delta variant spreading and people spending more time indoors in schools, for example—"I think the CDC should be recommending high-performance masks for everyone when they're in these risky indoor situations," she says.

"As N95s become more available, they can be worn in non-health-care settings; however, cloth masks are an acceptable and recommended option for masking."
—Jade Fulce

WHAT MAKES A GOOD MASK?

When it comes to mask effectiveness, the most important parameters are filtration, fit and comfort. Filtration generally refers to the percentage of particles the mask material blocks. For example, an N95 filters at least 95 percent of airborne particles. But that does little good if gaps around the mask let air in freely. A well-fitted mask should sit snugly against the face and over the chin, with no gaps around the nose or mouth. Comfort is also an extremely important metric: a mask does no good if people simply find it intolerable to wear.

A good mask is "the most important defense we have" against COVID, says aerosol expert Kimberly Prather, an atmospheric chemist at the University of California, San Diego.

There are a number of national standards for respirator quality. The U.S. gold standard, N95s, are certified by the CDC's National Institute for Occupational Safety and Health (NIOSH). And the Occupational Safety and Health Administration (OSHA) sets standards for how they have to fit people in work settings (such as in hospitals). But there is no official standard for N95 use by the general public. The European equivalent of the N95 is the FFP2 respirator, which filters at least 94 percent of particles. China has the KN95, and South Korea has the KF94. All provide excellent filtration, so it really comes down to which fits an individual best and is most comfortable.

WHICH MASKS ARE BEST?

In the absence of more specific guidance from health authorities such as the CDC as to which brands of respirators and other masks provide the best protection, some skilled amateurs have stepped in to fill the gap. Aaron Collins, aka "Mask Nerd," is a mechanical engineer at Seagate Technology with a background in aerosol science. In his free time, he makes YouTube videos in which he tests and reviews high-filtration masks made by various manufacturers. Collins says he does not earn any money from mask manufacturers or his videos themselves—he considers them a service and wants them to be objective.

Collins has a mask-testing setup in his bathroom, where he assesses masks' filtration efficiency by generating aerosols of sodium chloride (salt). He then uses a condensation particle

counter—a device that measures the concentration of particles inside and outside a mask he is wearing—to determine the total inward leakage through and around the mask. (For comparison, NIOSH's N95 standard requires manufacturers to measure leakage through the respirator material itself. And OSHA measures how a respirator fits on someone's face, which often involves wearing an N95 in an enclosed space with saccharin or another distinctly flavored test aerosol sprayed in: if the wearer reports tasting the substance, the mask fails the fit test.)

Collins also tests "pressure drop," which is basically how easy it is to breathe while wearing a mask. If doing so is too difficult, a wearer might not only find the mask less comfortable but also suck in air around its sides, negating its filtration. Some cloth masks—including those outfitted with coffee filters—have this problem. "There's a reason N95s aren't made from cloth," Collins says.

The Mask Nerd's top picks can be found in this video. In general, he recommends KN95s made by Chinese company Powecom and others, a variety of KF94s such as the Bluna FaceFit and N95s made by reputable brands such as 3M, Moldex or Honeywell. All of these masks had close to 99 percent filtration efficiencies and fairly low pressure drops in Collins's setup. (For comparison, he found that a surgical mask alone had between about 50 and 75 percent filtration efficiency, depending on the fit, and a good cloth mask had about 70 percent.) But when choosing the best mask, comfort should be a deciding factor, he says. Not everyone needs to wear an N95.

"To me, the minimum I want to see people wear is a KN95 or KF94 with the Delta variant," Collins says. "I don't think surgical masks are good enough anymore, and we should've gotten rid of cloth masks last summer—they're not even in the spectrum" of good filtration. (To be clear, some studies have found that surgical and cloth masks can provide at least some protection against COVID. A recent large, randomized study in Bangladesh found that surgical masks significantly lowered the risk of infection; cloth masks did not have a measurable benefit, although other studies suggest they provide some protection.)

THE BEST MASKS FOR KIDS

With children starting school in-person, many parents are understandably worried about their kids, especially those who are too young to be eligible for vaccination—and particularly in states where politicians have tried to ban mask mandates in schools. These parents might find Collins's recommendations for high-filtration kids' masks particularly helpful. There is no N95 standard for children, but plenty of manufacturers make KF94 or KN95 masks for them. Such masks are designed for small faces and are easy to put on. Collins sees no reason why kids could not tolerate them. "I have my own son," Collins says. "He's five years old. He wore them all summer."

WHERE TO FIND LEGITIMATE MASKS

An issue with commercially available high-filtration masks is that they may not come from reputable suppliers. The CDC's Web site warns that about 60 percent of KN95 respirators available in the U.S. are counterfeit. To find ones that are legitimate, Prather recommends the Web site Project N95. Masks can also be ordered directly from suppliers such as Bona Fide Masks, which sells KN95s made by Powecom. "That's the one people swear by," Prather says. They cost around $1 each. DemeTECH sells N95s for around $4 apiece, as well as other types of masks.

REUSING MASKS

One reason people may be reluctant to use KN95s and similar masks is because they are usually considered disposable. But several experts say they can in fact be worn multiple times. "You can probably reuse it until it becomes visibly damaged or soiled," Marr says. Collins's amateur testing suggests the masks can be used for up 40 hours with no decrease in their filtration efficacy (he recommends using them within six months of opening a package). The virus likely does not survive long on these masks, but it is not a bad idea to have a few in rotation, reusing one every three days or so, Collins says.

DOUBLE MASKING

One popular way to increase effectiveness is to wear a cloth mask on top of a surgical mask. This strategy, which the CDC has recommended, combines the filtration efficiency of the surgical mask material with the fit

of a cloth mask. But how well does it actually work?

According to Collins, pretty well. He measured a filtration efficiency of upward of 90 percent for a cloth mask (with nose wire) over a surgical mask. But the pressure drop was almost twice as high as that of an N95. One reason the CDC and others have recommended against the use of N95s by the general public, apart from their previous scarcity, is that they can be difficult to breathe through—so Collins finds it "baffling" that the CDC would recommend double masking. "So does double masking work? Yes, but … I think there are better solutions," he said in one of his videos.

Another way to get a better fit is to use masks with straps that go around the back of the head or to use a mask brace if one only has access to a surgical mask.

Not all experts agree that high-filtration masks are necessary for everyone. "What I usually say is 'the best mask is the one you wear properly,' " says Judith Flores, a pediatrician and a fellow of the American Academy of Pediatrics and of the New York Academy of Medicine. Flores believes surgical masks are the most convenient and cleanest option if they are discarded after each use. Cloth masks are okay, too, she adds, as long as they have three layers. "Unless you are a health-care worker or home care worker tending to a person who is COVID-positive," Flores says, "you don't need an N95."

FACIAL HAIR

What about the bewhiskered among us? How does facial hair influence the effectiveness of various masks? While there is not a great deal of data on this, some research suggests that the longer a person's beard or mustache is, the less effective a mask will be because it makes an inferior seal with the face. The CDC has released a somewhat amusing graphic demonstrating styles of facial hair that are appropriate to wear with a respirator.

At this point in the pandemic, with supplies of high-quality masks readily available in many areas, perhaps it is time to ditch loose-fitting cloth or surgical masks for something that provides better protection. "The most important layer of protection," Prather says, "is to never let the virus get out in the air in the first place."

—*Tanya Lewis*

Is This Food Really Healthy? New Packaging Labels Would Tell You

A simple traffic light symbol or a set of stars on the fronts of food products would advise consumers

Today's grocery store aisles are overflowing with "healthy," "whole grain" and "all natural" treats and snacks. But when you take a closer look at the nutrition facts and ingredients, some of these foods are actually packed with sugar, fat, salt or artificial flavors. To crack down on misleading claims, lawmakers recently introduced legislation called the Food Labeling Modernization Act of 2021, which would require and standardize a front-of-package labeling system that tells consumers if a product is healthy—or if it is not.

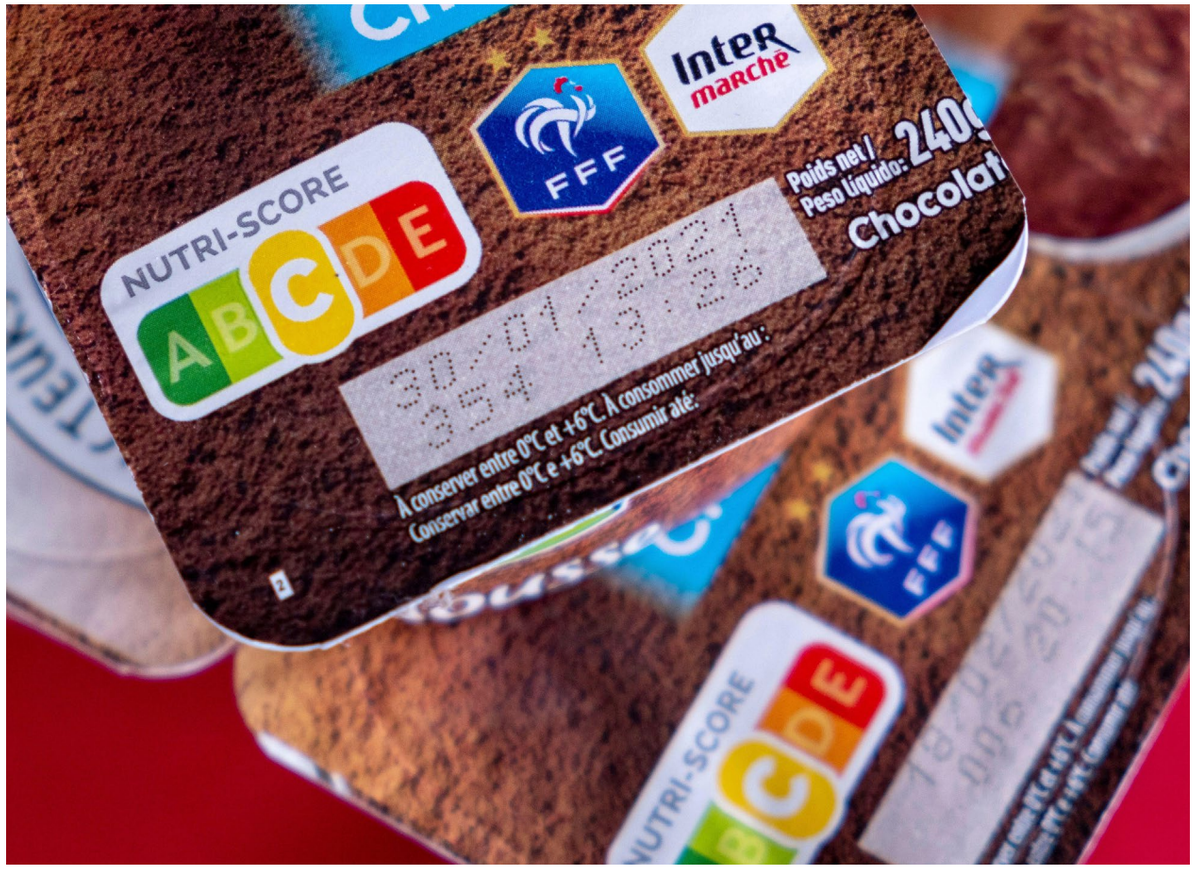
The labeling system would include an easily recognizable symbol that rates foods on healthiness. One option is a traffic light icon: the idea might be to make the light red if the food was full of sugars and fats, for example, green if it was low in fat and full of vitamins, and yellow if it was in between. Another system suggested in the bill would use stars: think five stars for a fiber-rich, low-calorie granola and one star for an artificially sweetened and colored cereal. If the product contained lots of saturated or trans fats, sodium or added sugars, there would be an additional warning on the label.

The bill includes further requirements for claims of certain ingredients. Any food item with the term "whole grain" on its packaging would have to clarify the actual percentage of whole-grain content. Products that said they contained fruits or vegetables—even those that just had images of an apple or tomato on their label—would have to clarify how much of these ingredients they included. These labels, the bill stipulates, would be standardized in how they looked and where they were located on a food's package, bag or box.

Supermarket shoppers are no doubt familiar with back-of-package nutrition-fact labels—those black-and-white boxes that declare how many calories, grams of sugar or milligrams of cholesterol, and quantities of other nutrients are

contained within one serving. The U.S. Food and Drug Administration required and standardized these labels in 1990 to better inform the public, but they do not always drive consumers to pick one food over another, says Jayson Lusk, an agricultural economist at Purdue University. A notification on the front can be more obvious and persuasive. "Research does suggest that front-of-pack labels have more impact on consumer choice than standard nutrition-fact labels," he says.

But there are pros and cons to such markers, Lusk explains. For one, some research shows that people do not always respond to them predictably. "You might see that a product has 'low sodium,' but that might signal to people, 'This tastes bad' " and dissuade them from purchasing it, he says. Another con is the difficulty in creating a one-size-fits-all definition. "People have very nuanced and conflicting perspectives on what 'healthy' means," Lusk says. Plus, there is limited real estate on the front of a packaged food, Lusk points out, so exactly how the labels would look and fit might impact their efficacy.



Packaged food sold in France includes letter-grade stoplight labels to rate products on nutritional value. Similar labeling schemes are proposed in new legislation recently introduced to the U.S. Congress.

The meaning of symbols might also get lost in a supermarket, which is often a chaotic and overstimulating place even for the savviest, most nutrition-conscious consumer, says David Just, an agricultural economist at Cornell University. Shoppers are "just looking for the gist of [whether] something is healthy or unhealthy," he says. Busy, multitasking people do not always have the time or bandwidth to read and consider complicated labels on the front of every product they throw in their cart, Just says. Most of that decision-making happens on a knee-jerk level, he explains.

That said, Just thinks the new bill does address a real problem "and could perhaps have a positive influence." Some countries in Europe have put stoplight labels on foods to grade them on their healthiness, similar to the new bill's proposal, he says. "We're not the only country dealing with this," Just says. In 2016 Chile passed a law mandating front-of-package warning labels. Although that requirement's direct effects on metrics such as obesity are not yet clear, some companies reformulated their products, removing sugar, salt or saturated fats out of their recipes to avoid warning labels.

Just and Lusk both point to successful efforts within independent grocery stores to implement stoplight or star systems that grade foods on nutritional value. "When we've seen simple systems like this put in place, it generally causes a pretty positive impact on shoppers who are a little less engaged in nutrition," Just says.

The Food Labeling Modernization Act, introduced by Representative Frank Pallone, Jr., of New Jersey on August 3, was assigned to the House Committee on Energy and Commerce for study and review. No further action has been scheduled for the food labeling legislation yet.

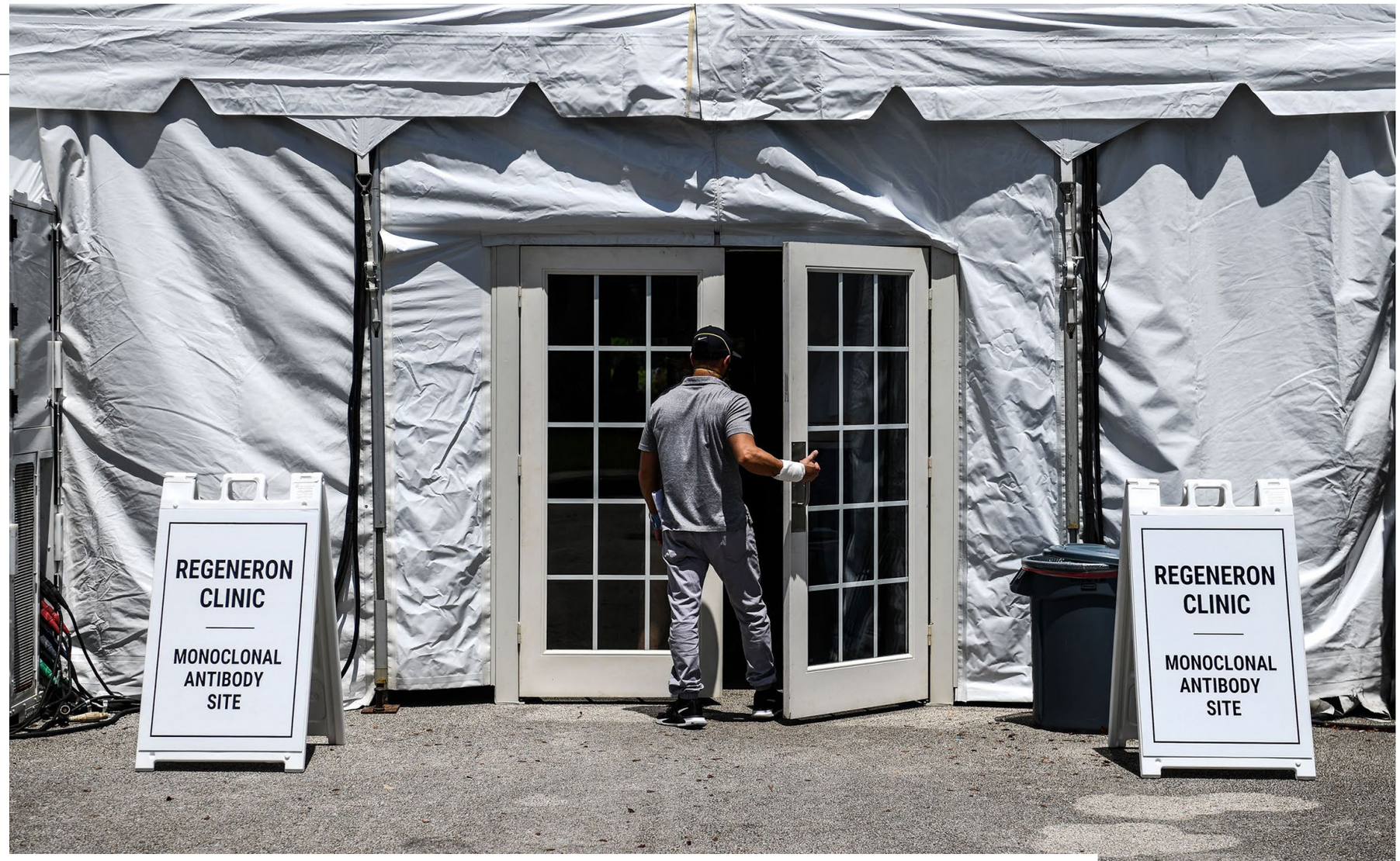
—Tess Joosse

Alamy

Do Monoclonal Antibodies Help COVID Patients?

Experts explain what this treatment involves, who needs it and how to get it

As COVID deaths continue to spike across the U.S.—primarily among unvaccinated populations—new treatments for the disease are again receiving attention. Monoclonal antibody (mAb) therapies are among the most effective. In this treatment, patients are infused with high concentrations of antibodies specifically engineered to fight SARS-CoV-2, the COVID-causing virus.



Man enters the Regeneron Clinic at a monoclonal antibody treatment site in Pembroke Pines, Fla., on August 19, 2021. Chandan Khanna *Getty Images*

These treatments have been particularly popular in states such as Florida, which has high numbers of unvaccinated people and has been suffering a major outbreak of the Delta variant since August. Governor Ron DeSantis, who has been dismissive of COVID vaccines as a personal choice without broader impact on society, has nonetheless touted mAbs, calling them "the best thing we can do to reduce the number of people who require hospitalization." Health officials argue that vaccination is a better way to avoid the need for these treatments in the first place. But mAbs are indeed effective when delivered early in an infection.

Florida has rolled out more than 20 nonclinical infusion centers—including libraries, theaters and churches—to administer mAbs to people who either have COVID or have been recently exposed to someone who does. Even so, public health workers have had trouble keeping up with demand—one viral photograph taken in late August shows a woman sick with COVID lying on the floor of the Jacksonville Library while awaiting a mAb injection. DeSantis said that more than 90,000 people have received the treatment as of September 16.

Scientific American talked with several experts about mAbs and how they fit into the fight against COVID.

What are monoclonal antibodies, and how do they work?

MAbs have long been used to treat diseases such as cancer and autoimmune disorders—the U.S. Food and Drug Administration has approved nearly 100 such treatments since

1994. To create them, researchers inject a protein—part of SARS-CoV-2, for instance—into a mouse and then collect some of its immune cells that create antibodies against the protein. These cells are then fused with human cancer cells and allowed to multiply so that the specific antibodies can be made at scale and infused into patients. Many mAbs for COVID seem to work best as a "cocktail" of antibodies that each target different parts of the virus.

The approved COVID mAbs appear to be most effective when given right after a person begins showing symptoms. "That's the time window in which the virus itself is playing a bigger role, before it triggers the inflammatory complications," says Brandon Webb, an infectious disease physician at Intermountain Healthcare in Utah. If a patient's immune system overreacts to the infection and requires artificial ventilation because of inflammatory damage to the lungs, the antibodies appear much less effective—and may even be harmful.

What antibodies are available?

Right now three mAb treatments that target SARS-CoV-2 are available under an FDA emergency use authorization (EUA), which allows a treatment to be used in certain people but stops short of full approval. An antibody called sotrovimab, made by GlaxoSmithKline and Vir, appears to reduce the risk that people infected with COVID will be hospitalized for more than a day or die by 79 percent. A two-antibody cocktail from Regeneron called casirivimab/imdevimab appears similarly effective, reducing the risk of hospitalization and death by 70 percent.

The FDA authorized a third cocktail—Eli Lilly's bamlanivimab/etesevimab—in 2021, but the Department of Health and Human Services paused its distribution earlier this year after it appeared to be ineffective against certain new viral variants. After a two-month hiatus, the cocktail is back on the market in states where fewer than 5 percent of COVID infections are from strains that are resistant to the treatment (currently this applies to all 50 states).

In June the FDA authorized a fourth cocktail, Genentech's tocilizumab, for people already hospitalized with COVID. Unlike the other therapies, which target SARS-CoV-2 itself, tocilizumab targets a signaling molecule that can cause the immune system to overreact and produce dangerous levels of inflammation. Back in 2010 the FDA approved tocilizumab for rheumatoid arthritis. It is only moderately effective against COVID, however: studies show that 12 percent of patients receiving the mAb required ventilation or died, compared with 19 percent of those receiving a placebo.

Who can get mAbs?

The antibodies from Eli Lilly, Regeneron, and GlaxoSmithKline and Vir are approved for children age 12 and older and adults who have not been hospitalized, whereas Genentech's antibodies are for children and adults who are already on ventilators. But not everyone can get the treatments right now: the EUAs stipulate that patients must be at high risk of complications from COVID to receive them. That includes people age 65 and older and those with conditions such as obesity, diabetes and cardiovascular disease.

In August the FDA authorized Regeneron's mAb for people who meet these risk criteria and have been exposed to COVID but have not yet tested positive.

What does the treatment entail?

In a clinical setting, mAbs are administered as an intravenous infusion—similar to a chemotherapy treatment—that lasts about 20 minutes. The Regeneron cocktail can also be injected under the skin. That is the preferred method at pop-up sites and nonclinical settings where intravenous infusions are difficult, says Susanne Doblecki-Lewis, an infectious disease physician at the University of Miami. In the injection method, four shots are given simultaneously, typically two in the arms and two in the stomach.

After administering the mAb treatment, clinics monitor patients for one hour for rare allergic reactions. Other side effects include hypersensitivity, rashes and diarrhea. Although patients do not need to pay for the mAb cocktail itself, some clinics bill for the infusion, which requires skilled health-care workers and specific equipment to administer.

Are mAb treatments a substitute for vaccination?

Both Webb and Doblecki-Lewis stress that mAb treatment is no substitute for vaccination. "Unfortu-

nately, the vaccine has become so political that some people would prefer monoclonal antibodies because of the way they're being promoted," Doblecki-Lewis says. But the vaccines have fewer side effects, are cheaper and more widely available, and are much easier to administer. "The vaccine is just so clearly a better step one," she says.

Vaccinated people with breakthrough COVID infections can get mAb treatments if they meet the EUA criteria. That includes people who are immunocompromised and thus unlikely to have had a strong immune response to the vaccine. Conversely, though, some evidence suggests that getting mAb treatment before getting the vaccine lowers the latter's ability to raise an immune response because the body already has high levels of antibodies against SARS-CoV-2. That is why the U.S. Centers for Disease Control and Prevention recommends that unvaccinated people who receive mAb treatment wait 90 days before receiving their first vaccine. But they should still get vaccinated, Webb says. "It's unrealistic to think we could treat our way out of this pandemic," he adds.

—*Sara Reardon*

Rogue Antibodies Involved in Nearly One Fifth of COVID Deaths

Self-targeting antibodies attack part of the immune system that plays a key role in fighting infection

Antibodies that turn against elements of our own immune defences are a key driver of severe illness and death following SARS-CoV-2 infection in some people, according to a large international study. These rogue antibodies, known as autoantibodies, are also present in a small proportion of healthy, uninfected individuals—and their prevalence increases with age, which may help to explain why elderly people are at higher risk of severe COVID-19.

The findings, published on August 19 in *Science Immunology*, provide robust evidence to support an observation made by the same research team last October. Led by immunologist Jean-Laurent Casanova of the Rockefeller University, the researchers found that around 10 percent of people with severe COVID-19 had autoantibodies that attack and block type 1 interferons, protein molecules in the blood that have a critical role in fighting off viral infections.

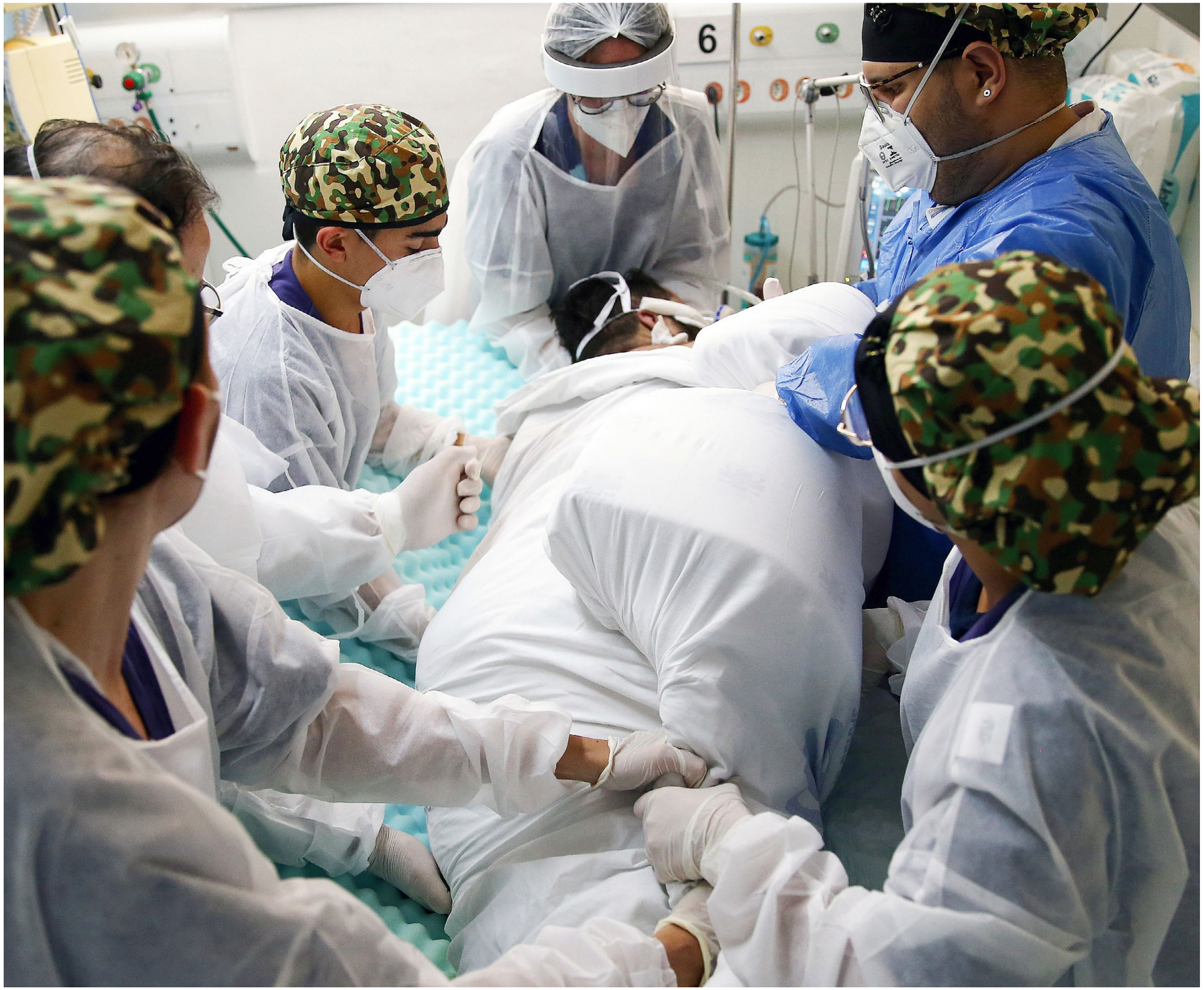
"The initial report from last year was probably one of the most important papers in the pandemic," says Aaron Ring, an immunologist at the Yale School of Medicine, who was not involved in this work. "What they've done in this new study is really dig down to see just how common these antibodies are across the general population—and it turns out they're astonishingly prevalent."

The international research team focused on detecting autoantibodies that could neutralize lower, more physiologically relevant concentrations of interferons. They studied 3,595 patients from 38 countries with critical COVID, meaning that the individuals were ill enough to be admitted to an intensive care unit. Overall, 13.6 percent of these patients possessed autoantibodies, with the proportion ranging from 9.6 percent of those below the age of 40, up to 21 percent of those older than 80. Autoantibodies were also present in 18 percent of people who had died of the disease.

Casanova and his colleagues suspected that these devious antibodies were a cause, rather than a consequence, of critical COVID. There were hints that this might be the case—the group had previously found that autoantibodies were present in around four in 1,000 healthy people whose samples had been collected before the pandemic. The team also found that individuals with genetic mutations that disrupt the activity of type 1 interferons are at higher risk of life-threatening disease.

To examine this link further, the researchers hunted for autoantibodies in a massive collection of blood samples taken from almost 35,000 healthy people before the pandemic. They found that 0.18 percent of those between 18 and 69 had existing autoantibodies against type 1 interferon and that this proportion increased with age: autoantibodies were present in around 1.1 percent of 70- to 79-year-olds and 3.4 percent of those over the age of 80.

"There is a massive increase in prevalence" with age, Casanova says. "This largely explains the high risk of severe COVID in people in the elderly population." He adds that these findings have clear clinical implica-



tions and suggests that hospitals should be checking patients for these autoantibodies, as well as mutations implicated in blocking type 1 interferons. This could identify people who are more likely to become critically ill from COVID, helping physicians to tailor their treatment appropriately.

A sample of more than 30,000 people is "too big to ignore," according to Ring. "It just shows that this is something that we need to think about." He adds that researchers should now consider whether autoantibodies play a part in driving other infectious diseases. Ring's team has already found evidence of autoantibodies against various immune system components in people with COVID, and he and his colleagues are now investigating further.

"I suspect that we've just started scratching the surface," Ring says.

—Diana Kwon

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Clinicians manually lie a COVID-19 patient prone in an ICU in São Paulo, Brazil.

Mario Tama *Getty Images*

Why Kids Beat Back COVID Better Than Adults

Innate immunity might be the key to why children have fared better with the virus. But the Delta variant poses fresh unknowns

By Smriti Mallapaty

Chris Gash

Smriti Mallapaty is a senior reporter at *Nature*.

EARLY LAST YEAR CHILDREN'S HOSPITALS ACROSS NEW YORK CITY HAD to pivot to deal with a catastrophic COVID-19 outbreak. "We all had to quickly learn—or semi-learn—how to take care of adults," says Betsy Herold, a pediatric infectious disease physician who heads a virology laboratory at the Albert Einstein College of Medicine. The reason: while hospitals across the city were bursting with patients, pediatric wards were relatively quiet. Children were somehow protected from the worst of the disease.

Data collected by the U.S. Centers for Disease Control and Prevention from hospitals across the country suggest that people under the age of 18 have accounted for less than 2 percent of hospitalizations caused by COVID—a total of 3,649 children between March 2020 and late August 2021. Some children do get very sick, and more than 420 have died in the U.S., but the majority of those with severe illness have been adults—a trend that has been borne out in many parts of the world.

This makes SARS-CoV-2 somewhat anomalous. For most other viruses, from influenza to respiratory syncytial virus, young children and older adults are typically the most vulnerable; the risk of bad outcomes by age can be represented by a U-shaped curve. But with COVID, the younger end of that curve is largely chopped off. It's "absolutely remarkable," says Kawsar Talaat, an infectious disease physician at the Johns Hopkins Bloomberg School of Public Health. "One of the few silver linings of this pandemic is that children are relatively spared."

The phenomenon was not entirely surprising to immunologists, however. With other viruses, adults have the advantage of experience. Through prior infection or vaccination, their immune systems have been trained to deal with similar-looking pathogens. The novelty of SARS-CoV-2 leveled the playing field and showed that children are naturally better at controlling viral infections. "We always think of children as germ factories," says Dusan Bogunovic, an immunologist and geneticist at the Icahn School of Medicine at Mount Sinai. But it's not because their immune systems are ineffective; they're just inexperienced, he says.

Research is beginning to reveal that the reason children have fared well against COVID could lie in the innate immune response—the body's crude but swift reaction to pathogens. Kids seem to have an innate response that's "revved up and ready to go," Herold says. But she adds that more studies are needed to fully support that hypothesis.

The emergence of the Delta variant has made finding answers more urgent. Reports suggest that in the U.S. and elsewhere, children are starting to make up a larger proportion of reported infections and hospitalizations. These trends might be because of Delta's high transmission rate and the fact that many adults are now protected by vaccines.

For now there is no clear evidence that children are more vulnerable to or more affected by Delta compared with earlier variants. But SARS-CoV-2, like all viruses, is constantly mutating and becoming better at evading host defenses, and that could make understanding childhood's protective benefits more important. "We haven't paid much attention to age-related differences in immune responses because it hasn't had huge clinical implications previously," says Lael Yonker, a pediatric pulmonologist at Massachusetts General Hospital. "COVID highlights that we need to better understand these differences."

BRAINSTORMING IDEAS

Why are children better than adults at controlling SARS-CoV-2? At first, researchers thought that children were simply not getting infected as often. But the data show that they are—at least nearly (children under age 10 might be slightly less susceptible).

The American Academy of Pediatrics found that, up until August, some 15 percent of all COVID cases in the U.S. had been in individuals aged under 21—that is more than 4.8 million young people. And a survey in India that tested people for antibodies against SARS-CoV-2, which are produced after infection or vaccination, found that more than half of children aged six to 17—and two thirds

of the population overall—had detectable antibodies.

Clearly, children are getting infected. So maybe the virus cannot replicate in them as well as it does in adults. Some researchers proposed that children might have fewer ACE2 receptors, which the virus uses to enter and infect cells. There is conflicting evidence on age-related differences in ACE2 expression in the nose and lungs, but scientists who measured the viral load—the concentration of viral particles—in people's upper airways have seen no clear difference between children and adults.

In one analysis of 110 children, posted as a preprint on June 3, researchers found that infants through to teenagers could have high viral loads, especially soon after being infected. "Not only is the virus there and detectable, but it's live virus," which means these individuals are also infectious, says Yonker, who led the study.

Another proposal is that children, who seem to be sniffling all year round, might be more exposed to other coronaviruses that cause the common cold and therefore have a squad of antibodies at the ready with some ability to latch onto the pandemic coronavirus. But the weight of evidence suggests that adults also have this immunity. Strikingly, these cross-reactive antibodies do not offer any special protection—if anything, they could lead to a misguided response.

Having largely discounted these hypotheses, Herold and her colleagues set out to look at whether there was something specific in children's immune response that gave them a benefit.

Some clues were circulating in the blood of those who have been infected. In a study comparing 65 individuals aged under 24 with 60 older people, Herold and her colleagues found that, overall, the younger patients (who had milder symptoms) produced similar levels of antibodies to the older cohort. But they had reduced levels of specialized antibodies and cells related to the adaptive immune response, the arm of the immune system that learns about a pathogen and helps to quickly quash it if it ever returns. Specifically, kids had lower levels of neutralizing antibodies that block SARS-CoV-2 from infecting cells; antibodies that label infected cells to be gobbled up and destroyed by other cells; and white blood cells known as regulatory and helper T cells.

"For us adults, it takes two days to ramp up the viral defense system to a level that we see from day zero with children. It's the time lag that makes the difference between children and adults."
—Roland Eils

In contrast, the children in the study had higher levels of the signaling proteins interferon-γ and interleukin-17, which alert the immune system to the arrival of a pathogen. These were probably produced by cells that line the airways and are involved in mediating innate immunity. Herold suspected that the children mounted a less robust adaptive immune response because their innate response was more efficient at eliminating the threat. An overactive adaptive response in adults, she says, could be causing some of the complications in COVID.

Another study, by researchers in Hong Kong, of adults and children infected with SARS-CoV-2 also found that the adaptive response—specifically that of T cells—was less potent in children, suggesting that something was happening early on that triggered the difference, says study coauthor Sophie Valkenburg of the University of Hong Kong.

But, she says, other factors such as reduced inflammation and a more targeted adaptive response could also be important. The researchers found that infected children had lower levels of cells known as monocytes, including inflammatory monocytes, which act as a bridge between the innate and adaptive immune systems. But these children did have higher levels of T follicular helper cells, which are important for making an early antibody response.

FIRST RESPONDERS

Herold and her colleagues have since tried to measure more directly the innate response in children. They took nose and throat swabs from people arriving at the emergency department, including 12 children with milder disease and 27 adults, some of whom died. The children had higher levels of signaling proteins such as interferons and interleukins and higher expression of the genes that code for such proteins.

One broad category of immune cells that could be playing an important part in children, Yonker says, are innate lymphoid cells, which are among the first to detect tissue damage and secrete signaling proteins that help to regulate the innate and adaptive immune responses. In one study posted as a preprint on July 4, Yonker and her colleagues found that the number of innate lymphoid cells in the blood of people who did not have COVID declined with age and was lower in men—mirroring the greater risk of severe disease observed in older men. Adults with severe disease and children with symptoms also had reduced levels of these cells.

Compared with adults, children recently infected with SARS-CoV-2 have also been found to have higher levels of activated neutrophils, cells that are on the front line in the response to unfamiliar invaders. Neutrophils ingest viral particles before they have a chance to replicate, says Melanie Neeland, an immunologist at the Murdoch Children's Research Institute (MCRI) in Mel-

bourne, Australia, who led the work. Furthermore, they become less effective with age.

Epithelial cells that line the insides of the nose could also be coordinating the quick response. In children, these cells are flush with receptors that can recognize molecules commonly found in pathogens; specifically, researchers have found that children have significantly higher expression of genes encoding MDA5, a receptor known to recognize SARS-CoV-2, than do adults. After spotting the viral intruder, these cells immediately trigger the production of interferons. "For us adults, it takes two days to ramp up the viral defense system to a level that we see from day zero with children," says study co-author Roland Eils, a scientist in computational genomics at the Berlin Institute of Health. "It's the time lag which makes the difference between children and adults."

Studies of rare, inherited, immune disorders also point to a predominant role for innate immunity in thwarting respiratory pathogens such as influenza.

Isabelle Meyts, a pediatric immunologist and physician at the Catholic University of Leuven in Belgium, regularly sees children with immune disorders. When the pandemic hit, she prepared a plan to protect them. "The patients I was most scared for were actually the patients who have innate immune defects," Meyts says.

Her hunch has so far proved correct. Children with disorders affecting their adaptive immune response—those who do not produce antibodies or have faulty B cell and T cell production, for example—did not encounter problems when infected with SARS-CoV-2. Among those who became severely ill were children with shortcomings in their innate immune response, she says. "It's not really the adaptive immune system that is helping you to beat this virus."

A study in adults also found that a small number of people with severe COVID have mutations that disrupt type 1 interferon activity, which plays a part in the innate immune response to viruses. Separate analyses found that one in 10 people with life-threatening COVID produced antibodies that blocked the activity of these interferons and that the prevalence of such antibodies increases with age in people who have not previously been infected with the coronavirus.

"Almost all viruses have developed ways of evading the innate immune system, and COVID-19 is no exception to that rule. Right now—knock on wood—the kids are still winning with their innate immunity. But for how much longer? We don't know."
—Betsy Herold

But, an overactive innate response might be detrimental as well. People with Down syndrome, for example, are more at risk of severe COVID, which Meyts says could be because the extra chromosome they have contains several genes involved in the type 1 interferon response. There is an intriguing balance to be struck between a deficient initial response and an excessive one, Meyts says. "It needs to be exactly right on the spot, and the timing needs to be perfect."

TICKLING BAD MEMORIES

Innate immunity is hardly the whole story, researchers say, especially given how interconnected it is with the adaptive response."The idea that the immunological tone is different in children seems likely," says Laura Vella, an immunologist and pediatric infectious diseases researcher at Children's Hospital of Philadelphia. "But what's contributing to that difference?" It could be many things working together, she says.

Some researchers propose that years of exposure to other human coronaviruses could mean that adult immune systems approach SARS-CoV-2 the way they would those other viruses, resulting in a less effective response—a concept known as original antigenic sin. In contrast, kids could be producing a fresh, more finely tuned response to a brand-new virus.

Amy Chung, an immunologist at the Peter Doherty Institute for Infection and Immunity in Melbourne, has seen some evidence of this in an expansive study of antibodies in the blood of a few hundred children and adults, including 50 infected with SARS-CoV-2. She and her colleagues found that adults had more cross-reactive antibodies targeted at parts of SARS-CoV-2 that were similar to bits of other coronaviruses, whereas children tended to produce a broader range of antibodies against all sections of the virus.

Researchers are also looking at other factors that are known to worsen with age, such as the ability to control inflammation and heal damaged tissue. Children are less prone to clots forming in blood vessels, and this could offer some protection, says Vera Ignjatovic, a biochemist who studies pediatric hematology at the MCRI.

Of course, not all children have asymptomatic or mild infection. Some, many of whom have underlying conditions such as chronic heart disease or cancer, get serious pneumonia. And estimates vary widely for the prevalence of long COVID, in which symptoms persist for months or more. A recent preprint suggested that up to 14 percent of young people who test positive for COVID have multiple symptoms three months after the diagnosis. And a small group of otherwise healthy kids—some three out of 10,000 infected individuals aged under 21—experience a condition known as multisystem inflammatory syndrome in children (MIS-C). They generally respond well to the ini-

tial infection but about a month later are admitted to hospital with a host of symptoms, from heart failure to abdominal pain and conjunctivitis, with minimal damage to the lungs. “It’s a sick group of kids,” Vella says.

Michael Levin, a pediatrician and infectious diseases physician at Imperial College London, thinks MIS-C is probably the result of an outsized antibody or T cell reaction to the infection. But despite hundreds of papers on the topic, “exactly what distinguishes children who get MIS-C from the rest of the child population is completely unknown,” Levin says.

As the pandemic wears on, researchers worry that the virus could evolve in ways that thwart some part of kids’ innate protection. Some researchers have found that the Alpha variant, which was dominant in some parts of the world for a time, developed tricks that allowed it to suppress the body’s innate immune response. They worry that Delta could do the same. For now increased hospitalizations of children in regions where Delta is circulating seem to be the result of its enhanced infectivity across all ages, coupled with the fact that many adults are vaccinated or have already been infected with SARS-CoV-2. But researchers are watching carefully.

“Almost all viruses have developed ways of evading the innate immune system, and COVID-19 is no exception to that rule,” Herold says. “Right now—knock on wood—the kids are still winning with their innate immunity. But for how much longer? We don’t know.” SA

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COVID Vaccines Show No Signs of Harming Fertility or Sexual Function

The novel coronavirus, in contrast, can disrupt both things in unvaccinated men and women

By Emily Willingham

Pregnant woman receives a dose of the Pfizer-BioNTech vaccine against COVID-19 at a vaccination center in Bogotá, Colombia, on July 23, 2021.

Raul Arboleda *Getty Images*

Emily Willingham is a science writer and author of *Phallacy: Life Lessons from the Animal Penis* (Avery, Penguin Publishing Group, 2020). Her book *The Tailored Brain: From Ketamine, to Keto, to Companionship: A User's Guide to Feeling Better and Thinking Smarter* will be published in December 2021 by Basic Books.

Rumors and myths about COVID-19 vaccine effects on all aspects of reproduction and sexual functioning have spread like a Delta variant of viral misinformation across social media platforms, where people swap rumors of erectile dysfunction and fertility disruptions following vaccination. Yet studies so far have not linked the vaccines with problems related to pregnancy, menstrual cycles, erectile performance or sperm quality. The evidence does show that COVID can involve problems in all of these areas.

Health officials have tried to ease concerns by explaining that data from clinical trials and hundreds of millions of vaccinations support the safety of the shots. *Scientific American* spoke with four experts in reproductive and sexual biology about pervasive myths, the evidence against them and the real damage to health caused by COVID. Below is a series of conclusions that can be drawn from studies of vaccinated people and those who have had the disease.

Vaccination is not associated with adverse effects in pregnancy. COVID-19 is the real threat.

The U.S. Centers for Disease Control and Prevention updated its recommendations in early August, strengthening its advice that people who are pregnant or breastfeeding should be vaccinated against COVID.

The U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) found in August that "there is no pattern … to suggest that any of the COVID-19 vaccines used in the U.K. increase the risk of congenital anomalies or birth complications. Pregnant women have reported similar suspected reactions to the vaccines as people who are not pregnant."

If infected with the virus, pregnant people are at highly increased risk for severe disease and complications from COVID, compared with their same-age counterparts, says Tara Shirazian, an associate professor and a gynecologist at N.Y.U. Langone Health.

The immune system effects of pregnancy itself make an infection about five times more likely, says Jane Frederick, a reproductive endocrinology and fertility specialist and medical director of HRC Fertility in California. "You get infected more quickly, and pregnant women can go downhill fast," she adds.

People should take the opportunity to get vaccinated before conceiving, but the vaccine is safe across all three trimesters of pregnancy, says Mary Rosser, director of integrated women's health at the department of obstetrics and gynecology at Columbia University Irving Medical Center. In early August, 22 medical groups released a joint statement saying that "the best way for pregnant individuals to protect themselves against the potential harm from COVID-19 infection is to be vaccinated."

The vaccines show no fertility effects, including among people using assisted reproductive techniques.

One origin of fertility falsehoods about the vaccines may be a letter co-written by a former Pfizer researcher and sent to the European Medicines Agency (EMA) in December 2020. The two authors asked that all vaccine studies be suspended. They claimed that vaccine-induced antibodies against a protein that SARS-CoV-2 uses to enter human cells might also attack another human protein needed for embryo implantation. SARS-CoV-2 is the virus that causes COVID.

A study published in June 2021 compared the success of transferring embryos to women who carried antibodies to SARS-CoV-2 after vaccination or infection to success rates among those without antibodies. The pres-

ence of antibodies did not appear to affect such rates during 171 transfer attempts.

In a *New York Times* essay, a pair of immunologists described their work showing that the sequences of amino acids that make up the implantation-related protein and those that make up the virus spike protein are not similar and that spike-targeting antibodies do not cross-react with the implantation protein.

Stress may be responsible for menstrual cycle problems following vaccination.

Some vaccinated women have reported disruptions to their monthly cycle. "We are not dismissing them," Rosser says. "What they say about their own bodies is important, and they know their bodies best."

But nothing in the vaccines is a likely candidate to explain these complaints. Experts agree that a probable indirect factor is stress. Getting a new vaccine is itself stressful, Shirazian says, and many kinds of stressors can throw off a menstrual cycle. The physiological effects of these tensions might disrupt pathways that drive menstrual timing.

The good news, Rosser says, is that any menstrual effects appear to be transient. "I've talked to enough women in the past eight months, and it seems as though whatever it is, it's short-lived," she says.

In early August EMA released a report noting that no cause-and-effect association had been established between complaints of menstrual disruptions and COVID vaccination. Separately, MHRA found no link between menstrual disorders and COVID vaccines.

Some descriptions of menstrual problems mention clotting during heavier periods. Shirazian says that the term "blood clot" as it relates to menstrual flow is different from the term used medically to describe a clot in a blood vessel. "They have nothing to do with each other," she says. The clotting of menstrual blood happens as the blood exits the vessels and is not a risk for blocking flow to tissues.

"Illness causes stress. And next to any menstrual cycle disruptions that might follow vaccination, it's 100 percent worse to have COVID, if you had to choose between the two."
—Tara Shirazian

COVID-19 may affect the menstrual cycle.

Becoming ill with COVID is associated with clotting in the medical sense—producing pulmonary embolisms that block blood flow to the lungs, for instance. Some evidence also points to the effects of SARS-CoV-2 on menstrual cycles. A small study of 177 patients who had COVID, published in September 2020, showed that 28 percent experienced cycle disruptions, including less bleeding and a longer cycle.

Infectious diseases themselves also are a stressor, Rosser says. "Illness causes stress," she adds. And next to any menstrual cycle disruptions that might follow vaccination, "it's 100 percent worse to have COVID, if you had to choose between the two," Shirazian says.

Vaccines do not threaten sperm or erectile function, but COVID-19 does.

Ranjith Ramasamy, director of reproductive urology at the University of Miami, has published several studies describing the novel coronavirus in penile and testicular tissue and its effects on erectile dysfunction. He and his colleagues also looked at the potential effects of vaccines in these areas and found none.

To Ramasamy, the most unsurprising observation was how COVID interferes with erections, which rely on blood flow. "COVID affects the blood vessels that supply organs, and the penis is not much different from other organs that require a lot of blood," he says.

What was more surprising was the presence of SARS-CoV-2 in penile tissue even nine months after an infection. These results were from a small study of people with penile implants because of severe erectile dysfunction. The rich blood supply to the penis seems to have ensured a route for the virus to these tissues, Ramasamy says.

Like many viruses, SARS-CoV-2 also finds its way into the testes, where it can enter cells and cause damage. A biopsy study of testis tissue from six people who died of COVID showed the virus still lingering in a sample from one of the patients and decreased sperm counts in another three. A sample from a patient who had survived the disease also showed persistent SARS-CoV-2 in the testes.

Ramasamy and his colleagues have found no detrimental changes in sperm counts and other fertility measures after vaccination. "One of the biggest myths with the vaccine was that it could affect fertility," he says, and finding no negative effect on sperm counts "was very reassuring."

Some last words on vaccination and the ill effects of COVID-19.

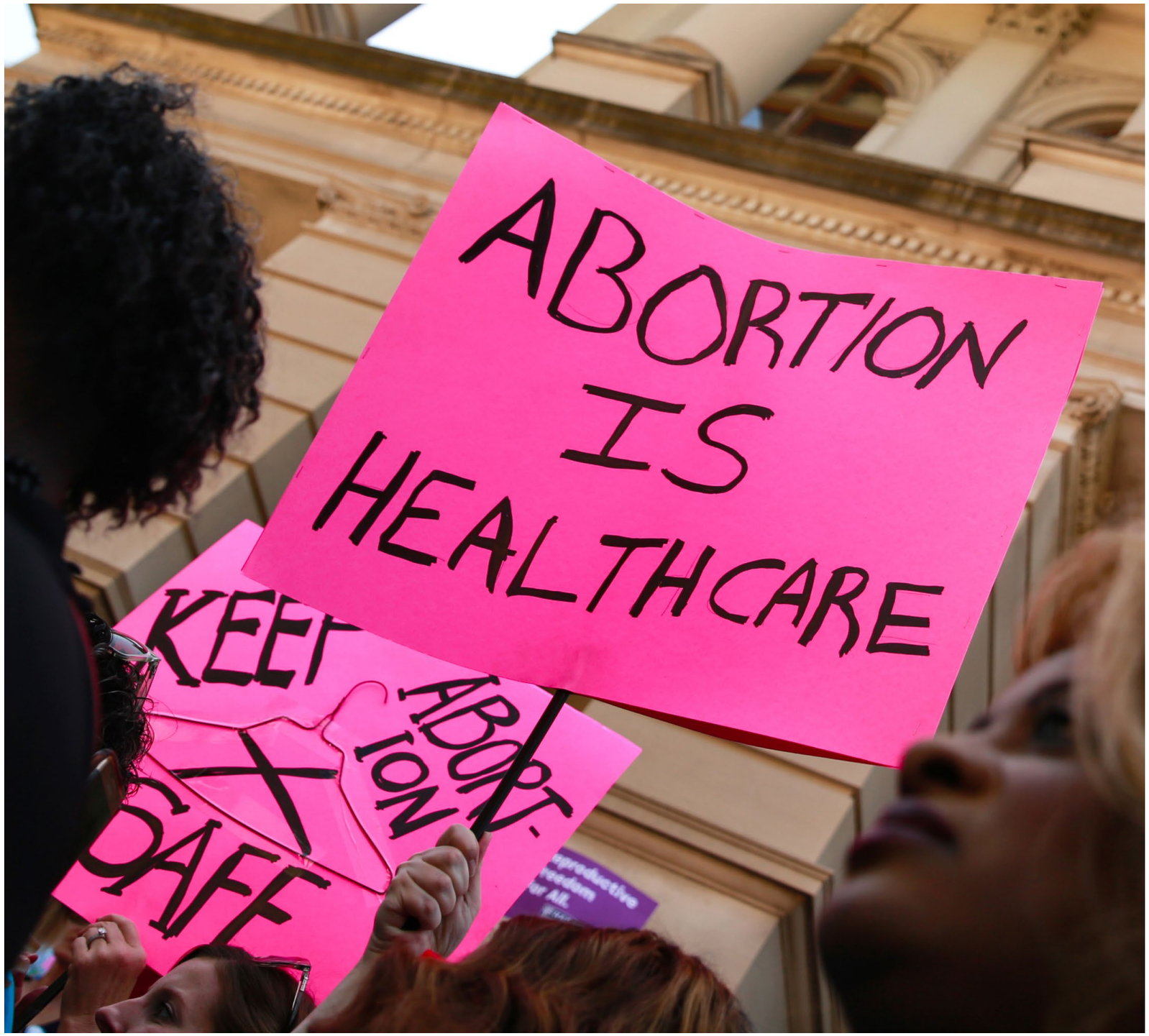
All of the experts had the same take-home message: the key to protecting against the reproductive and sexual effects of COVID is to get vaccinated. SA

Michelle Rodrigues is a a primatologist/biological anthropologist in the department of social and cultural sciences at Marquette University. She studies comparative primate social behavior and endocrinology, including stress in monkeys, apes and humans.

REPRODUCTION

The Absurd Pregnancy Math behind the "Six-Week" Abortion Ban

The law the U.S. Supreme Court just failed to block is not just a blow to women; it's biologically nonsensical



Elijah Nouvelage *Getty Images*

The Supreme Court recently upheld a Texas law that would prevent patients from accessing abortion care after six weeks of pregnancy. There are many reasons this law is concerning—chiefly that it will do considerable harm to many people—but it is also based on bad biology. Pregnancy math is confusing, and it's unclear whether legislators involved are simply ignorant on reproductive biology or recognize that it's an indirect way to ban all abortions.

But in reality, the six-week ban limits abortion care to only four weeks after conception and only one week, realistically, from when a person could find out they are pregnant. At this stage, an embryo

has implanted and has a neural tube, and the blood vessel that will develop into the heart begins pulsing. This pulsing, or "heartbeat," is the basis for the emotional appeal of these bills. But at this early stage, the embryo is still in the process of differentiating organs and won't be classified as a "fetus" until about a month later.

The reason pregnancy math works so strangely is practical: it's easier to pinpoint the first day of someone's last period and count from that point as a standard marker because dates of ovulation and conception are harder to identify. But counting pregnancy as beginning during the last period includes two weeks prior to actual pregnancy and can inspire public health policy considering all women of reproductive age to be "prepregnant," such as health messages that recommend that all women of reproductive age abstain from alcohol. Given a lack of adequate education in health and biology—educational information that is often another target for evangelical Christians—some may think "six weeks of pregnancy" is plenty of time to realize you are pregnant. But at only four weeks postconception and three weeks post-implantation, there is a limited window to even affirm pregnancy.

This is where pregnancy math meets menstrual math, which is further complicated by the limits of hormonally detecting pregnancy. Menstrual math, or predicting when a "missed" period occurs, is often based on an assumed 28-day cycle. If you have a regular 28-day cycle, the expected missed period should happen two weeks after conception. That gives you about two weeks before that "six-week" threshold to take a pregnancy test and see your doctor. But it's recommended that you wait for a week after your missed period to take a pregnancy test because if you take it too early, you may get a false negative result. Pregnancy tests measure human chorionic gonadatropin (hCG), a hormone produced after implantation. Although it can be potentially detected shortly after implantation, at about a week after conception and "three weeks" pregnant, it may not build up to detectable levels until a couple of weeks later. Thus, for patients with a predictable 28-day cycle, there is only about one week before the "six-week" threshold to confirm pregnancy. For someone who knows they want an abortion, taking a test, getting confirmation from a health-care provider and having the abortion would have to occur within a single week.

But most people who menstruate do not have a regular 28-cycle. That neat, four-week cycle is a simplification of a more variable process. One study found about 13 percent of women have that "typical" 28-day cycle. The average is close to it, but it varies within a range of about 21 to 40 days and may not be consistent from month to month. A person with an average cycle length of 29 days may have a cycle that is 27 days one month, 29 another and 31 another. If their period hasn't arrived "on time," they may not notice until it's been a week late.

Imagine another person with a 35-day cycle. Ovulation and conception may not even occur until "three weeks of pregnancy." The earliest they may be able to detect a pregnancy is at "four to five weeks" pregnant. They won't be expecting their period until "five weeks" and may not even remark it as a late period until "six weeks." By the time they have taken a pregnancy test, they have been carrying that embryo in their body for only three weeks, and they have already missed the window to access abortion. Such variability in cycle may be even more common for adolescents, perimenopausal woman, transgender men receiving gender-affirming hormonal treatments, and people undergoing other health crises or significant stressors.

There are many reasons someone may want an abortion, and often detection of pregnancy happens after that six-week threshold. This Twitter thread provides heartbreaking examples, including abuse victims, children as young as 11, trans men grappling with dysphoria and women with wanted pregnancies that were not viable.

Ultimately these decisions should be between pregnant people and their doctors, not politicians. In the Catholic tradition I was raised in, I was taught that the soul begins at conception—but also that dogs do not have souls. Both those theological positions are now recognized as less certain by Pope Francis. American evangelical opposition to abortion is tightly entangled with white supremacist ideas about outreproducing other racial and religious groups. Everyone should have the right to follow their own religious convictions—but legislators' personal beliefs should not dictate medical decisions between a pregnant person and their health-care provider.

Maia Szalavitz is a journalist and author or co-author of seven books. Her latest, *New York Times* best seller *Unbroken Brain: A Revolutionary New Way of Understanding Addiction*, was published in April 2016 by St. Martin's Press.

BEHAVIOR

The FDA Shouldn't Support a Ban on Kratom

The herbal supplement can be misused, but given the explosion in opioid deaths, eliminating this safer substitute will almost certainly lead to more deaths

In ordinary times, there would be no question about whether a drug with opioidlike effects should be proven safe and effective and approved by the Food and Drug Administration before it is widely marketed. But these aren't ordinary times, and the herbal supplement kratom is not a typical drug.

In fact, the issue of whether or not to ban kratom is an excellent litmus test of whether the Biden administration will actually use the philosophy of harm reduction to guide drug policy—or just spout the trendy catchphrase as window dressing to hide ongoing engagement in the war on drugs.

An estimated 10 million to16 million Americans currently use kratom as an alternative to opioids, most commonly to treat pain or as a substitute for street drugs. The herb, formally known as *Mitrogy-*

A worker in Indonesia examines a sample of ground kratom leaves.

Dimas Ardian *Getty Images*

na speciosa, has a centuries-long history of use in herbal medicine in Southeast Asia—notably as a substitute for opium. It is typically sold as a bitter-tasting powder, which can be made into a tea or swallowed in capsules.

Because kratom never drew enough international attention to spur an American or global prohibition, our lax regulation of "health supplements" made from plants allows it to be sold legally here. Sales have risen sharply in recent years, as both pain patients and people with addiction have increasingly lost access to medical opioids during the overdose crisis.

Kratom does appear to be far safer than all illegal and most prescription opioids: a CDC study of some 27,000 overdoses that occurred between 2016 and 2017 found that it was implicated in less than 1 percent of deaths. Given the large number of people who regularly use it and the low number of fatalities, researchers estimate that it is more than 1,000 times less likely to kill than typical prescription opioids.

Moreover, in nearly all overdose deaths associated with kratom, it was accompanied by stronger drugs that kill more often, so it is not clear that it actually played a major role or even any at all. For example, around two thirds of the 152 deaths the CDC studied also involved illicit fentanyl and its analogues, which are thousands of times more potent. In only seven cases was kratom the only substance identified—and even here researchers cannot rule out the possibility of undetected drugs.

Regardless of the specific facts about particular drugs, however, for more than 100 years the main strategy America has used to deal with drug problems is prohibition. With the exception of alcohol, caffeine and tobacco, nearly every substance that has publicly been associated with recreational use has either been banned entirely or strictly confined to medical use. Prohibition policy—such as the war on drugs—assumes that restricting drug sales and possession will solve the problem, period.

In contrast, when policy makers are guided by harm reduction, they have to assess whether banning a specific drug or allowing continued sales will do more damage—in the current context of other drugs for which it may substitute and other factors such as harms associated with arrest and incarceration.

For example, in a country where no one was misusing stronger opioids and no one was already using kratom, introducing it without controls could well be harmful. But in the context of an America with the highest number of overdose deaths ever—driven largely by street fentanyl—removing a safer substitute almost certainly will increase mortality.

Unfortunately, kratom prohibition may be coming: the FDA is now asking for public comment about whether the U.S. should support an international ban on the drug, which the United Nations, through the World Health Organization, is considering.

The agency's own position is clear: it opposes over-the-counter sales of kratom as a health supplement and wants its sales to be illegal unless it is proven medically effective. An international ban would automatically require the U.S. to prohibit the drug domestically, under its treaty obligations.

In concert with the Drug Enforcement Administration, the FDA previously has sought to ban kratom. In 2016 the DEA announced that it planned to place kratom into Schedule I of the Controlled Substances Act—the category intended for drugs that have potential for misuse and have no medical use. Along with drugs such as cocaine, this is where marijuana, MDMA (ecstasy) and LSD currently languish; the classification itself makes research to determine medical usefulness extremely difficult, creating somewhat of a catch-22.

But for what is apparently the first time since the Harrison Act of 1914 legally enshrined drug prohibition, consumers successfully fought back. The DEA had no problem getting the media and Congress terrified of LSD and MDMA when those drugs became popular in the 1960s and 1980s, respectively. By 2016, though, both journalists and elected officials were far more skeptical of the usefulness of prohibitions—and probably not incidentally, kratom sales had by then become a billion-dollar industry. The proposal was dropped.

The FDA, however, still seems to want it off the market. In its call for public input about whether the drug should be globally banned, it described the herb this way:

"Kratom is abused for its ability to produce opioid-like effects.... Kratom is an increasingly popular drug of abuse and readily available on the recreational drug market in the United States. Evidence suggests that kratom is abused individually and with other psychoactive substances.... In the United States, kratom is misused to self-treat

chronic pain and opioid withdrawal symptoms."

Kratom supporters and the industry see this as the agency's attempt to bypass its previous failure to win direct support for a domestic ban. In comments made to Marijuana Moment, a policy newsletter, Mac Haddow of the American Kratom Association (AKA) argued that the agency's intent to support a worldwide prohibition was an "abuse" of its authority, adding, "More overdose deaths will occur if kratom is banned, and that is exactly what the FDA is trying to do."

Ideally, we would have a responsive regulatory system that allowed for the approval of the safest medical and recreational drugs—one that based its decisions on relative harms rather than on moral panics that are more associated with fears about race, class and ethnicity than actual drug effects.

But in our current system, it's certainly understandable that the FDA would seek to ban kratom: the only alternative for a substance that has risks and can cause a high is prohibition or regulation as a medicine, which cannot be done without clinical trials for safety and efficacy first.

If we are genuinely to enact harm reduction policy, we have to change this. Banning a substance that does less harm than other widely available substitutes will make things worse. President Joe Biden's policy needs to be more flexible; otherwise it will increase harm rather than reducing it.

Nora D. Volkow is director of the National Institute on Drug Abuse at the National Institutes of Health.

BEHAVIOR

Drug Overdose Deaths in 2020 Were Horrifying

We need radical change to address the crisis

The provisional drug overdose death statistics for 2020 confirmed the addiction field's worst fears. More people died of overdoses in the U.S. last year than in any other one-year period in our history. More than 93,000 people died. The increase from the previous year was also more than we've ever seen—up 30 percent.

These data are telling us that something is wrong. In fact, they are shouting for change.

It is no longer a question of "doing more" to combat our nation's drug problems. What we as a society are doing—putting people with drug addiction behind bars, underinvesting in prevention and compassionate medical care—is not working. Even as we work to create better scientific solutions to this crisis, it is beyond frustrating—it is tragic—to see the effective prevention and treatment tools we already have just not being used.

Robert Lang *Getty Images*

The benefits of providing effective substance use disorder treatments—especially medication for opioid use disorder—are well known. Yet decades of prejudice against treating substance use disorders with medication have greatly limited their reach, partly accounting for why only 18 percent of people with opioid use disorder receive medications. Historical reluctance to provide these treatments and of insurers to cover them reflects the stigma that has long made people with addiction a low priority.

We must eliminate the attitudes and infrastructure barring treating people with substance use disorders. This means making it easier for clinicians to provide lifesaving medications, expanding models of care such as digital health technologies and mobile clinics that can reach people where they are and ensuring that payers cover treatments that work.

The science of the matter is unequivocal: addiction is a chronic and treatable medical condition, not a weakness of will or character or a form of social deviance. But stigma and long-standing prejudices—even within health care—lead decision makers across health care, criminal justice, and other systems to punish people who use drugs rather than treat them. That approach may be simpler than asking us as a society to have compassion or care for people with a devastating, debilitating, often fatal disorder. But the risk of incarceration does not deter drug use, let alone address addiction; it perpetuates stigma and disproportionately harms the most vulnerable communities.

Evidence-based harm reduction, such as syringe services programs, also needs to be a part of any solution to our drug crisis, because this approach has been shown to reduce HIV and hepatitis C transmission and help link people to treatment for addiction and other conditions. Although the federal government has embraced evidence-based harm-reduction programs, many communities continue to resist them, erroneously thinking they sanction or encourage drug use. Multiple independent studies have shown that they don't. Researchers are also evaluating innovative but historically controversial strategies operating abroad such as centers for overdose prevention, where people can use substances under medical supervision and access other health services, to evaluate cost-effectiveness and ability to reduce deaths and improve health.

Part of the failure of the current approach to the drug crisis arises from the unrealistic expectation that people should—and can—just stop using drugs. Little concern is shown for people with addiction unless and until they are drug-free, but the reality is that difficulties and resumed use typically mark the recovery journey. Compassion, care and support need to extend to those still using drugs and those who return to drug use, not just to those who can satisfy the stringent standards of abstinence. Everyone with a substance use disorder, regardless of whether they are currently using drugs, needs good health care and may also need help with housing, employment and child care needs.

To prevent young people from misusing drugs and to keep people from all ages from developing substance use disorders, our nation must address the social and economic stressors that increase the risk of drug use, such as poverty and housing instability, unsafe neighborhoods and schools, and other effects of a changing economy, including social isolation and despair. Drug overdose deaths are one component of the "deaths of despair" that, along with suicide and alcohol-related illness, have caused life expectancy to decline in the U.S., even before the 1.5-year drop in 2020 caused largely by the COVID-19 pandemic.

On the ground, evidence-based interventions can make a big difference: universal prevention programs as well as interventions targeted to the most at-risk families and youth not only reduce the risk of later drug taking and addiction but have radiating benefits on other aspects of mental and physical health.

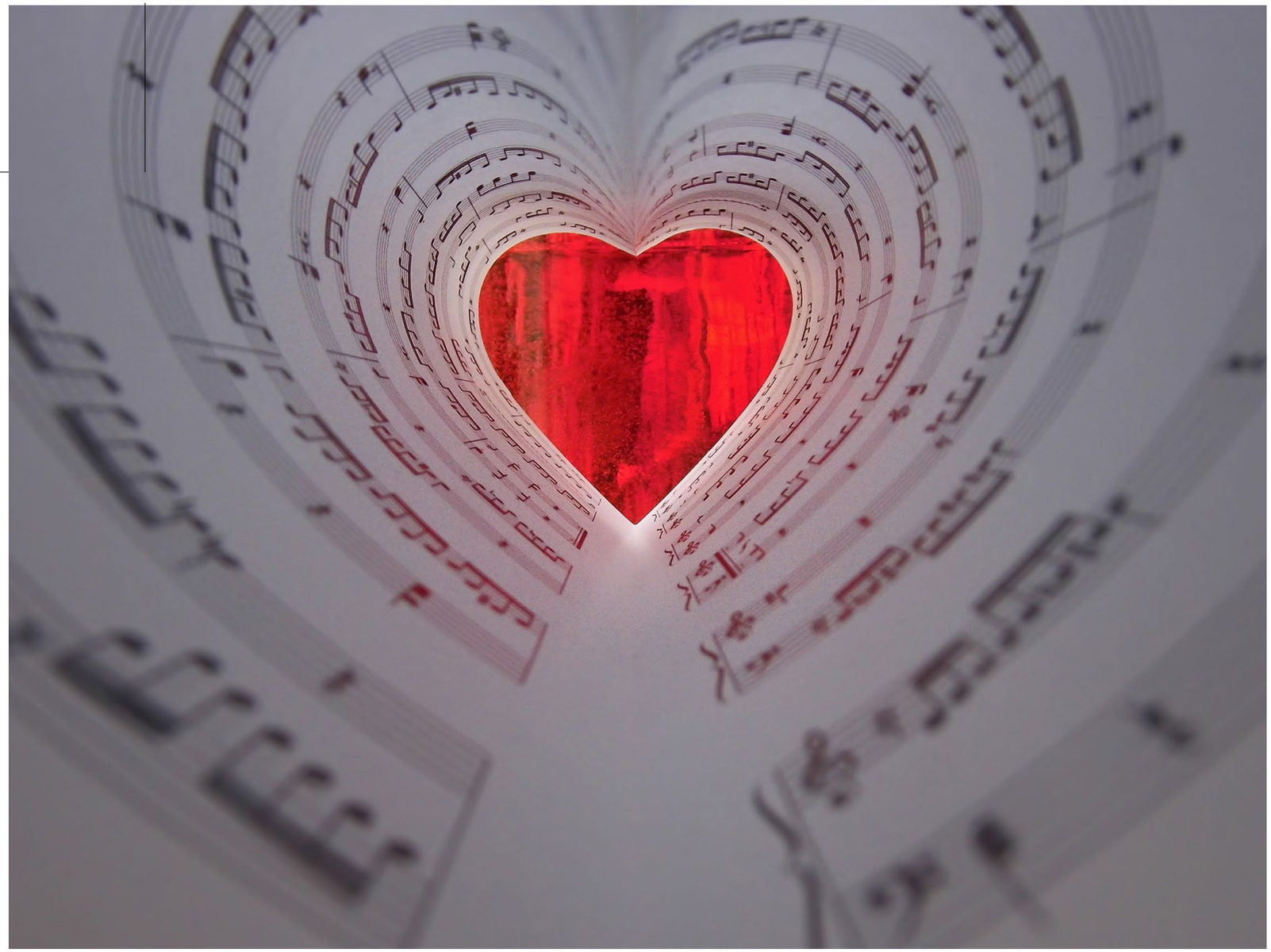
This poses a question of collective willingness to invest in these measures. The long-term savings in health care and justice costs relative to the costs of prevention interventions can be substantial. But they are long-term investments with benefits that will take time to accrue, and the nature of our society is to look at short-term bottom lines and expect immediate results.

Radical change to save lives is long overdue. It is crucial that scientists help policy makers and other leaders rethink how we collectively address drugs and drug use, looking to the evidence base of what improves health and reduces harm across communities and funding research to develop new prevention and treatment tools.

MEDICINE

How Music Can Literally Heal the Heart

Its structural attributes and physiological effects make it an ideal tool for learning cardiology, studying heart-brain interactions and dispensing neurocardiac therapy



Dragan Todorovic *Getty Images*

In a maverick method, nephrologist Michael Field taught medical students to decipher different heart murmurs through their stethoscopes, trills, grace notes and decrescendos to describe the distinctive sounds of heart valves snapping closed, and blood ebbing through leaky valves in plumbing disorders of the heart.

Separately, in music based on electrocardiographic (ECG) traces of heart rhythm disorders, one of us—musician-mathematician Elaine Chew—used music notation to capture the signature rhythms of electrical anomalies of the heart. Collaged from extant music fragments matching the heartbeats, Brubeck's *Blue Rondo à la Turk* provided the 2:4:3 rhythmic tattoo of ventricular early beats; Piazzolla's *Le Grand Tango* remixed produced the irregular rhythms of atrial fibrillation; *Little Etudes for piano,* with pedagogical descriptions by cardiologist Pier Lambiase, provided a layperson's introduction to electrical aberrations of the heart.

The reason these heart-music mappings work is because abnormal heart rhythms tend to form simple interbeat-interval ratios. In fact, the distinctive rhythms in Beethoven's music so closely resemble those of heart rhythm disorders that cardiologists have speculated that they may be transcriptions of Beethoven's possible arrhythmia, his interoceptive awareness of his own heartbeat enhanced by his deafness.

This is but one of multiple reasons music should be part of every heart physician's tool kit. Music and the heart have been romantically linked in popular consciousness because of their shared connections to human emotions and the brain. History is replete with examples of emotionally charged events followed almost immediately by

the death of the person. Surgeon John Hunter famously pronounced, "My life is at the mercy of any scoundrel who should put me in a passion," before collapsing and dying after a heated board room meeting.

Cardiologists Peter Taggart and Pier Lambiase have been studying how emotions alter the conductive properties of individual heart cells. Mental stress changes the recovery period of heart cells after each heartbeat, called the action potential duration. Taggart co-authored a study in which patients whose hearts were paced at a steady rate watch the harrowing "cut the rope" scene from *Vertical Limit* (2000). The patients' action potential duration shortened under the stress. This may explain how more extreme stress coupled with underlying cardiac disease could precipitate life-threatening arrhythmias.

Acute stress produces dramatic effects in the heart, but slow-burning chronic stress caused by protracted insecurity also predisposes sufferers to disease and mortality. The sympathetic nervous system's default state of high alertness is suppressed when safety is perceived; these safety brakes are lifted under duress. The "Generalized Unsafety Theory of Stress" co-written by psychophysiologist Julian F. Thayer links the unconsciously perceived unsafety of prolonged stressors such as low social status, early life adversity or loneliness to hypervigilance that increases the odds of developing heart disease.

Music moves us in part because it draws on our primal intuitions about the heartbeat. Until the mid-19th century when it was replaced by the mechanical metronome, the human heartbeat provided the standard unit of measure for musical time. In his 1496 treatise, the *Practica Musicae*, composer-theorist Franchinus Gaffurius wrote that the proper measure of the musical beat should be the pulse of a healthy human, noting that the pulses of "fevered persons" undergo an increase or become unequal in ways that worry physicians.

When we connect to the pulse of the music, we sense another's physiological states. The steady pulse at the beginning of Schubert's *Trio, Op. 100*, sets a strong but serene pace for its haunting melody. The breathless octaves in the opening of *Der Erlkrönig* evoke the rapid heart palpitations of the fevered boy in his father's arms, galloping through the stormy, windswept night. Hearing just heartbeats, pulse-only music has been found to increase listeners' ability to sense what others are feeling in a study co-authored by musician-scientist Grace Leslie.

Music changes our heart rates, breathing and blood pressure and alters our heart rate variability, indicators of cardiac and mental health. Neuroscientist Psyche Loui and her colleagues have traced music-induced physiological changes to a central node in the brain's networks, called the anterior insula, with dense connections to the vagus nerve, responsible for unconscious regulation of body functions.

The anterior insula is associated with empathetic mirroring of external and internal experiences. It is also connected to parts of the brain responsible for hearing (the auditory cortices) and for pleasure (the dopaminergic reward system). These auditory and reward network pathways most likely subserve the mind's ability to form predictions and expectations during music listening. The systematic fulfilment and violation of expectations are thought to underlie emotion and meaning in music.

Music is an ideal catalyst for inducing physiological changes in heart-brain studies because it can be dissected systematically into features based on note content and the way this content is communicated in performance. Evidence suggests that these musical attributes trigger brain responses at a basic level. Analyzing listeners' brain-imaging data in the OpenFMRI Study Forrest data set, composer-neuroscientist Michael Casey found that specific music features induced predictable activation patterns in regions of listeners' brains. The activation patterns were consistent enough for machines to infer the music the listener heard or its genre simply from their functional MRI scans.

Music features have also been linked to physiological responses. In a study co-authored by physicians Luciano Bernardi and Peter Sleight, loudness increases in vocal and orchestral music produced vascular constriction and blood pressure increases proportionate to these crescendos. Verdi arias with 10-second-long phrases—the period of Mayer waves, the body's natural blood pressure oscillation—caused listeners' heart and respiratory signals to sync with the music envelope. Such unconscious physiological responses are thought to be the progenitors of music-induced emotions.

Music also has a communal impact on human

physiology. People listening to the same music tend to synchronize not only their movements but also their breathing and heart rhythms. Some of this heartbeat coherence is from breathing together, but partial coherence (linear relationships) remained higher between the heartbeats of people vocalizing long notes together, over the baseline or breathing together, even after removing the effect of respiration.

The cognitive and physical demands of playing music also have measurable effects on musicians' heart rhythms and breathing patterns. Psychologists Caroline Palmer and Shannon Wright showed that repetitiveness of musicians' heart rhythms show greater rigidity (predictability) when playing unfamiliar musical melodies and also when playing first thing after waking in the morning rather than in the evening.

For cardiac patients, music-based interventions can also modulate cerebral blood flow, reduce preoperative anxiety and postoperative stress, improve surgery outcomes and lower cortisol levels. Music interventions are found to significantly affect heart rate and blood pressure in coronary heart disease patients. Listening to relaxing music reduced not only heart and respiration rates but also oxygen demand of the heart in patients who have had a heart attack.

Technological advances in biofeedback sensors means that physiological parameters like heartbeats and heart rate variability can be harnessed to guide music interventions in cardiac therapy. Physiological feedback can be used to select or shape music to influence listeners' heart rates and breathing, for example, to increase heart rate variability. With widespread adoption of biofeedback devices, the tailoring of music interventions to individual cognitive or neural-cardiac states is now well within reach enabling a "musical prescription" for improved mental and physical well-being.

Elaine Chew is a pianist-mathematician and principal investigator of the European Research Council–funded project COSMOS at the French National Center for Scientific Research, where she is based at the Sciences and Technologies of Music and Sound Laboratory located at the Institute for Research and Coordination of Acoustics/Music.
Psyche Loui is a neuroscientist-violinist and an associate professor and director of the Music, Imaging, and Neural Dynamics Laboratory at Northeastern University.
Grace Leslie, a flutist, electronic musician and scientist, is an assistant professor of music technology at the Georgia Institute of Technology, where she directs the Brain Music Laboratory.
Caroline Palmer is Canada Research Chair in the Cognitive Neuroscience of Performance and a professor of psychology at McGill University, where she directs the Sequence Production Laboratory.
Jonathan Berger is Denning Family Provostial Professor of Music and a Bass University Fellow in undergraduate education at Stanford University and a composer-researcher at the Center for Computer Research in Music and Acoustics.
Edward W. Large is director of the Music Dynamics Laboratory and the Theoretical Neuroscience Laboratory at the University of Connecticut, where he is a professor in the department of psychological sciences and the department of physics.
Nicolò F. Bernardi is a personal and professional coach and consultant who is trained as a cognitive neuroscientist, music therapist and yoga teacher.
Suzanne Hanser is chair emerita and professor of music therapy at the Berklee College of Music and president of the International Association for Music & Medicine.
Julian F. Thayer, a bassist and composer, is Distinguished University Professor in the department of psychological science at the University of California, Irvine, and Ohio Eminent Scholar Professor in Health Psychology emeritus at the Ohio State University.
Michael A. Casey is a professor in the department of computer science and the department of music at Dartmouth College.
Pier D. Lambiase is professor of cardiology at University College London Institute of Cardiovascular Science and Barts Heart Center and co-director of cardiovascular research at Barts Health NHS Trust.

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