phenomenon the 'Tony Fauci index'.

Fauci has been at the helm of the US National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, under seven US presidents, starting with Ronald Reagan in 1984. Most recently, he became the face of the US response to the COVID-19 pandemic and a trusted voice worldwide who helped millions to make sense of a rapidly evolving threat. During his tenure, he transformed NIAID from a lesser-known NIH institute with an annual budget of US$350 million to a global role model in infectious-diseases research with a budget exceeding $6 billion a year.

'Determined and aggressive' efforts

Fauci is one of the most highly cited scientists of all time on account of his work on HIV immunology, and has been well known in the infectious-diseases research community for decades. However, his role as a leading expert has, at times, been tumultuous. During the AIDS epidemic in the 1980s and early 1990s, activists felt that NIAID's clinical trials were moving too slowly to help people with HIV gain access to lifesaving therapies that were still being tested. They blamed Fauci for what they saw as unnecessary deaths, and staged protests in front of his office. Fauci began a dialogue with the activists that led, within years, to the development of effective treatments to suppress the virus that would become the global standard of care. This type of collaboration with the community was unprecedented and became a model for future health-care leaders, says Steven Deeks, an HIV clinician at the University of California, San Francisco. "But Tony was the first," he says.

Working with former president George W. Bush, Fauci also helped to design the US President's Emergency Plan for AIDS Relief (PEPFAR), a global programme launched in 2003 to provide treatment for people with HIV. PEPFAR, which is probably Fauci's greatest and most impactful accomplishment, Deeks says, has "unequivocally saved millions of lives". Bush awarded Fauci the Presidential Medal of Freedom in 2008 for his "determined and aggressive efforts".

In 2014, when people were worried about whether the Ebola outbreak in West Africa would become a pandemic, Fauci treated and hugged a nurse who had been infected with the virus and hospitalized at the NIH. Fauci later said he did this to show his staff that he wouldn't ask them to do anything that he wouldn't do himself. That "extraordinary level of empathy" will be difficult to replace, Nuzzo says.

Fast forward to 2020, and Fauci once again came under fire — this time from the president under whom he was serving. Dissatisfied with Fauci's guidance for curbing the spread of the coronavirus SARS-CoV-2 by implementing interventions such as mask wearing and social distancing, then-president Donald Trump attempted to silence Fauci by, at times, preventing him from speaking publicly. Trump also hinted that he might sack Fauci (Fauci is a civil servant in the US government, not a political appointee, so it is not clear how Trump might have done this). Fauci has received death threats and has had federal guards protecting him.

"Because of the sustained attacks on him and failure of our political leaders to rebuke those attacks, his ability to communicate was lessened," Nuzzo says.

The next generation

In announcing his departure, Fauci did not detail his future plans, but he was clear that he would not be retiring. "I plan to pursue the next phase of my career while I still have so much energy and passion for my field," he wrote. He indicated that whatever he does next will involve advancing science and public health, and mentoring the next generation of science leaders.

Fauci's mentorship has helped to shape countless scientists — including Akiko Iwasaki, an immunologist at Yale University in New Haven, Connecticut — into the scientists they are today. Iwasaki says that although she was just a "lowly postdoc" at the NIH in 1998, Fauci took time out of his schedule to meet her on several occasions. "He has this way of elevating scientists around him," she says.

NIAID did not respond to an e-mail enquiring about when Fauci's replacement might be named. But Deeks hopes that the new director will have the same desire to end the HIV epidemic. "Tony has carried this on his shoulders for 40 years," he says.

WHICH COVID BOOSTERS TO TAKE: A GUIDE FOR THE PERPLEXED

A diverse menu of vaccine options leaves people searching for the best route to protection.

By Heidi Ledford

The next generation of COVID-19vaccines is on its way, but those shots will be looking to take a seat at an already crowded table.

On the menu in some countries over the next few months will be the familiar standards — mRNA and protein vaccines based on the spike protein from the ancestral version of SARS-CoV-2, which ushered in the pandemic. Alongside them will be a smattering of new specials, including mRNA vaccines with spike sequences both from the ancestral virus and from Omicron variants.

It is a luxury of choice that many countries don't have. But the range of options, which will be available at different times, has left people wondering which vaccines to take, and when. "These are hard questions, and there are no real right answers," says Kathryn Edwards, a paediatrician and director of the Vanderbilt Vaccine Research Program at Vanderbilt University Medical Center in Nashville, Tennessee.

Nature asked specialists what evidence is on hand to help make the decision.

What's known about Omicron-specific COVID-19 vaccines?

Relatively little. On 15 August, the United Kingdom authorized the use of a two-pronged, or 'bivalent', vaccine containing both ancestral and Omicron BA.1 sequences of the spike protein, which the virus uses to latch onto human cells. The country's Joint Committee on Vaccination and Immunisation recommended the bivalent vaccine as one option in the country's autumn booster programme.

But the newer Omicron variants BA.4 and BA.5 now dominate in the United States and Europe. As a result, US regulators have said they intend to bypass BA.1-specific vaccines and instead authorize COVID-19 vaccines that include spike sequences from BA.4 and BA.5.

Vaccines stimulate the production of antibodies that can 'neutralize' SARS-CoV-2 — that is, stop it from infecting host cells. Laboratory data suggest that the inclusion of BA.1 sequences boosts neutralization of Omicron about twofold[1,2], but it's unclear how much, if any, extra protection against illness this will produce. Neutralization data for BA.4- and BA.5-specific vaccines aren't expected until around mid-September.

The underwhelming results for the bivalent vaccine are probably due to a phenomenon known as immune imprinting, says microbiologist John Moore at Weill Cornell Medicine in New York City. By now, much of the population has either been vaccinated or infected with an earlier variant of SARS-CoV-2. The immune system has therefore been trained to remember

VLADIMIR ZIVOJINOVIC/GETTY

Health-care workers wait to administer doses of COVID-19 vaccine.

this variant — and a dose of vaccine, even one with Omicron-specific components, will tend to boost those earlier immunological memories. The degree of Omicron-specific response will be relatively small, says Moore.

"If we had an immunologically naive population of people who had not been infected or vaccinated, it would make absolute sense for the vaccine to be from the Omicron lineage," he says. "But how many people are neither infected nor vaccinated?"

Should I take a standard booster or wait for an Omicron-specific one?

In some countries, people eligible for a mid-year booster have been wrestling with a decision: take a booster shot of one of the original vaccines, or wait a few more months for a version containing Omicron-specific spike.

Several physicians told *Nature* that the decision should be a personal one, and people should consider factors such as whether they're at risk of serious disease and how well they can shield themselves from SARS-CoV-2. "It's a lot of individual decision-making," says Meagan Deming, an infectious-disease specialist at the University of Maryland School of Medicine in Baltimore.

It also depends on how long people need to wait for the Omicron-specific vaccine, says Angela Branche, an infectious-disease specialist at the University of Rochester Medical Center in New York. "If you asked me two or three months ago, I'd have said the Omicron-specific version of the vaccine is several months away, get your booster now," she says. Now, the wait might be only about a month, so she is more willing to advise her low-risk patients to hold out for new vaccines.

Yet, others argue that there is still no need to delay a booster even a few weeks for the sake of receiving a new vaccine that might not edge out the old ones. "There's so little potential advantage to having an Omicron booster," says Moore. "Why bother, when you can use the existing booster sooner?"

How long should I wait between COVID-19 vaccine boosters?

Here, researchers are largely in agreement: it's best to wait at least four months between doses. Receiving a booster sooner does not cause harm, but there's probably little benefit.

One study found a weaker antibody response to vaccination in people who had high antibody levels before their shot than in people with lower levels of pre-vaccination antibodies[3]. This is no surprise, says study author and viral immunologist Pablo Penaloza-MacMaster at Northwestern University Feinberg School of Medicine in Chicago: "If the vaccines are given in a very short period of time, without allowing a resting period, you're minimizing the effect," he says.

Can you get too many boosters?

As long as the boosters are sensibly spaced, there's really no such thing as "too many" from an individual standpoint, says Moore. From a public-health standpoint, however, a focus on boosting everyone could shift resources away from the people who most need boosters: those over 50 years old, and people with pre-existing health conditions.

Boosters can significantly decrease the risk of serious disease for these groups. For younger people without risk factors, a booster's benefits are smaller, but a person who was boosted shortly before an infection might shed less virus into the community than someone whose antibody levels are lower when they are infected, says Penaloza-MacMaster.

Still, such a benefit is likely to be less meaningful than the benefit for people at risk of serious illness, says Moore. "The value for the under-50s in good health is far less certain," he says. "That's going to be a lower priority from a public-health perspective."

1. Chalkias, S. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.06.24.22276703 (2022).
2. Branche, A. R. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.07.12.22277336 (2022).
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