Prabhakar's nomination, saying her experience and leadership skills would serve the administration well.

"She is a natural leader," says Neal Lane, a physicist at Rice University in Houston, Texas, who served as director of the US National Science Foundation (NSF) while Prabhakar was at NIST, and went on to become Clinton's science adviser.

Although the position of science adviser does not require Senate confirmation, the role of head of the OSTP does – and that could take months. Since Lander's departure, sociologist Alondra Nelson has led the OSTP; at the same time, geneticist Francis Collins has been temporarily filling in as science adviser. Previously, Nelson had been serving as deputy director for science and society at the OSTP, a post to which she will now return; Collins stepped down as leader of the US National Institutes of Health in 2021.

One lesson from Lander's tenure is that behaviour matters, says Rebecca Barnes, a biogeochemist at Colorado College in Colorado Springs, and a leader of 500 Women Scientists, an organization that opposed his appointment as science adviser. And one lesson from Prabhakar's appointment is that diversity and accomplishment can go hand in hand, Barnes says. "I think it's important to diversify what a scientist looks like and what a scientist does," she adds. Prabhakar's appointment does both, and could help "change the face of science".

As much as anybody, Prabhakar has what it takes to address any lingering tensions from the Lander era and help the agency move forwards, says Margaret Levi, director of the Center for Advanced Study in the Behavioral Sciences at Stanford University in California. "She's an amazing manager who has dealt with very complex situations in the past."

Silo breaker

Born in New Delhi and raised in Lubbock, Texas, Prabhakar has led a distinguished career full of firsts, earning respect from scientists in academia and industry. In 1984, she earnt an applied physics PhD at the California Institute of Technology (Caltech) in Pasadena – the first woman to do so. And less than a decade later, she became the first woman to lead NIST, an agency that focuses on the development of scientific standards and tools.

In 2018, Prabhakar launched her own organization, Actuate, a non-profit think tank based in Palo Alto, California, that seeks to design scientific and policy solutions to global problems such as climate change. After her nomination was announced, the organization released a statement saying that Prabhakar will step down as chief executive once the Senate confirms her as head of the OSTP.

Speaking about scaling up innovative energy technologies and policies at a climate seminar at Caltech this month, Prabhakar demonstrated her thinking on how to promote transformational change. One problem in scaling up new technologies is that everybody – from technology and financial firms to government regulators – is operating independently, she said. To solve problems fast enough to make a difference to Earth's climate requires "breaking out of those silos".

Levi says that breaking down silos is one of Prabhakar's talents. "She's very engaged with how to make science and technology work to advance public policy on significant societal challenges."

Challenges ahead

Since taking office last year, Biden has laid out ambitious plans to boost innovation across the federal government and in the private sector. Some parts of his agenda are now moving forwards, but others – particularly in the areas of energy and climate – remain mired in a politically deadlocked US Congress. As both science adviser and head of the White House's core science agency, Prabhakar could have a key role in convening officials across the government and crafting science policies to facilitate progress.

One of the Biden administration's biggest science initiatives aims to boost innovation in biomedical research by creating the Advanced Research Projects Agency for Health. The agency is being modelled on DARPA, with the goal of promoting risky – but potentially rewarding and transformative – research. To ensure US competitiveness as nations such as China step up their investments in science, the administration has also established a new directorate in the NSF, an agency long dedicated to the funding of basic research, that will focus on supporting applied technology.

Biden and his fellow Democrats in Congress have already secured tens of billions of dollars for clean energy and climate initiatives, including an estimated US$22 billion for demonstration projects at the US Department of Energy. But many of Biden's climate-innovation efforts are tied up in a spending package that remains stalled among legislators.

Michael Lubell, a physicist at the City College of New York who tracks federal science-policy issues, says that Prabhakar is a sound choice for advancing the Biden agenda, which puts a premium on applied science. However, he worries that if the pendulum swings too far in that direction, it could begin to undermine basic-research programmes. "She is very good," he says, "but I'm a little concerned."

Others see opportunity. Lane says that Prabhakar has a unique background that should allow her to step up to multiple challenges. Whether the issue is bringing agencies together to confront climate change or confronting questions about research raised by a shifting relationship with China, Prabhakar's job will be to help build consensus and marshal the troops, he says.

"It takes somebody with the personal skills, and the knowledge and the respect that she will have coming into this job," Lane says.

WHAT THE LATEST OMICRON SUBVARIANTS MEAN FOR THE PANDEMIC

BA.4 and BA.5's rise seems to stem from their ability to infect people who were immune to earlier lineages.

By Ewen Callaway

Like a Hollywood franchise that churns out sequel after mind-numbing sequel, Omicron is back. Mere weeks after the variant's BA.2 lineage caused surges globally, two more Omicron spin-offs are on the rise. First spotted by scientists in South Africa at the start of the year, and linked to a rise in cases there a few months later, BA.4 and BA.5 are the newest members of Omicron's growing family of coronavirus subvariants. They have been detected in dozens of countries worldwide.

The BA.4 and BA.5 subvariants are spiking globally because they can spread faster than other circulating subvariants – mostly BA.2, which caused a case surge earlier this year. But so far, the latest Omicron subvariants seem to be causing fewer deaths and hospitalizations than their older cousins – a sign that growing population immunity is tempering the consequences of surges of the disease.

What are BA.4 and BA.5?

The two subvariants are more similar to BA.2 than to the BA.1 strain that kicked off most countries' Omicron waves late last year. But BA.4 and BA.5 carry their own unique mutations, including changes called L452R and F486V in the viral spike protein that might tweak its ability to latch onto host cells and

MORTEZA NIKOUBAZL/NURPHOTO VIA GETTY

BA.4 and BA.5 seem to be causing fewer hospitalizations than previous Omicron variants.

skirt some immune responses. A May preprint[1] found that BA.4 and BA.5 share an origin with earlier Omicron strains. But an unpublished analysis led by evolutionary geneticists Bette Korber and William Fischer at Los Alamos National Laboratory in New Mexico suggests that they are probably offshoots of BA.2.

Korber and Fischer also found that many genome sequences that are classified as BA.2 in public databases are actually BA.4 or BA.5. As a result, researchers could be underestimating the subvariants' ongoing rise, as well as the diversity of mutations carried by them. "It is important in this particular moment in the pandemic to get these calls right," Korber and Fischer wrote in an e-mail to *Nature*.

Why are the variants on the rise?

Variants' transmission advantages can result from biological changes that speed infection, for instance, allowing the virus to infect more people, more quickly.

But the rise of BA.4 and BA.5 seems to stem, instead, from their capacity to infect people who were immune to earlier forms of Omicron and other variants, says Christian Althaus, a computational epidemiologist at the University of Bern. With most of the world outside Asia doing little to control SARS-CoV-2, the rise — and inevitable fall — of BA.4 and BA.5 will be driven almost entirely by population immunity, Althaus adds, with cases increasing when protection lulls and falling only when enough people have been infected.

On the basis of the rise of BA.5 in Switzerland — where BA.4 prevalence is low — Althaus estimates that about 15% of people there will get infected. But countries are now likely to have distinct immune profiles because their histories of SARS-CoV-2 waves and vaccination rates differ, Althaus adds. As a result, the sizes of BA.4 and BA.5 waves will vary from place to place. "It might be 5% in some countries and 30% in others. It all depends on their immunity profile," he says.

What impact will BA.4 and BA.5 have on society?

This, too, is likely to vary by country. Despite high case numbers, South Africa experienced only a small rise in hospitalizations and deaths during its BA.4 and BA.5 wave, says Waasila Jassat, a public-health specialist at the country's National Institute for Communicable Diseases in Johannesburg.

In a study that will soon be posted to the medRxiv preprint server, Jassat and her colleagues found that South Africa's BA.4 and BA.5 wave led to a similar rate of hospitalization but slightly lower death rate when compared with the country's earlier Omicron wave. Both Omicron surges proved much milder, in terms of hospitalizations and deaths, than the country's ferocious Delta wave.

Outside South Africa, other countries are seeing more considerable impacts from BA.4 and BA.5. In Portugal — where COVID-19 vaccination and booster rates are very high — the levels of death and hospitalization associated with the latest wave are similar to those in the first Omicron wave (although still nothing like the impact caused by earlier variants).

One explanation for the difference could be Portugal's demographics, says Althaus. "The more elderly people you have, the more severe [the] disease." Jassat thinks that the nature of a country's immunity can also explain varying outcomes. About half of adult South Africans have been vaccinated, and just 5% have taken up a booster. But this, combined with sky-high infection rates from earlier SARS-CoV-2 waves, has erected a wall of 'hybrid immunity' that offers protection against severe disease.

How well do vaccines work against the variants?

Laboratory studies[2–6] consistently suggest that antibodies triggered by vaccination are less effective at blocking BA.4 and BA.5 than they are at blocking earlier Omicron strains, including BA.1 and BA.2. This could leave even vaccinated and boosted people vulnerable to multiple Omicron infections, scientists say. Even people with hybrid immunity, stemming from vaccination and previous infection with Omicron BA.1, produce antibodies that struggle to incapacitate BA.4 and BA.5. Research teams have attributed that to the variants' L452R and F486V spike mutations.

One explanation for this is the observation that BA.1 infection after vaccination seems to trigger infection-blocking 'neutralizing' antibodies that recognize the ancestral strain of SARS-CoV-2 (on which vaccines are based) better than they recognize Omicron variants[2,7]. "Infection with BA.1 does induce a neutralizing antibody response, but it appears to be a little bit narrower than one would expect," leaving people susceptible to immune-escaping variants such BA.4 and BA.5, says Ravindra Gupta, a virologist at the University of Cambridge, UK.

What will come next?

That's anybody's guess. The parade of Omicron subvariants could continue, with new variants picking further holes in existing immunity. "Nobody can say BA.4/5 is the final variant. It is highly probable that additional Omicron variants will emerge," says Kei Sato, a virologist at the University of Tokyo. Researchers have identified several spots on the spike protein that are currently recognized by the antibodies that are triggered by vaccination and previous infection, but that could mutate in future Omicron strains[2].

Another possibility is the emergence of a variant from a different branch of the SARS-CoV-2 family tree from the one that bore Omicron. Repeat Omicron infections could build broad immunity against successive lineages, creating an opening for a totally different SARS-CoV-2 variant that is unfamiliar to people's immune responses, says Gupta. "The bar is getting higher and higher for a virus to take over."

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