a risk to countries outside where it originated and if it requires an international response — meaning, in some cases, that it could have pandemic potential.

With each PHEIC, the WHO advises governments on how to deal with the emergency. For example, last January, WHO director-general Tedros Adhanom Ghebreyesus said of the COVID-19 outbreak, "It is still possible to interrupt virus spread, provided that countries put in place strong measures to detect disease early, isolate and treat cases, trace contacts and promote social-distancing measures."

What's in a name?

Liu admits that the term PHEIC isn't as sexy as an emotive word, such as 'pandemic' or 'emergency'. But researchers and health officials chose it partly because they wanted to avoid panic while encouraging world leaders to act according to WHO advice, says Gian Luca Burci, an international law specialist at the Graduate Institute of International and Development Studies in Geneva, Switzerland. Burci helped to revise the regulations in 2005.

In hindsight, that reasoning seems to be flawed. Several reports note that politicians and the public mainly ignored the PHEIC declaration and Tedros's corresponding recommendations in January 2020, but started listening when the organization used the unofficial term 'pandemic' to describe COVID-19 in March, once the disease was spreading on multiple continents. Unlike the PHEIC, 'pandemic' is not a defined declaration, and countries haven't agreed to take any actions once it's used.

Despite the disproportionate response to the word pandemic, many scholars argue that changing the name of the WHO's highest alarm wouldn't be useful. "I don't care for the term PHEIC," says Alexandra Phelan, a global-health lawyer at Georgetown University in Washington DC, "but I worry that if we get too into the words, we miss the point that countries need to act appropriately when there is a declaration."

Global-health scholars question why a PHEIC for COVID-19 wasn't declared sooner. On 22 January 2020, Tedros convened a closed-door meeting of virologists, public-health researchers and certain government representatives — as the PHEIC process dictates. They decided that a warning wasn't warranted, but a week later, the committee flipped its position. The delay might have cost the world time to contain the virus.

Still, a one-week lag in declaring a global emergency isn't even the most concerning action that took place in the early days of the COVID-19 pandemic, critics say. When Tedros declared the PHEIC, he advised governments to move fast with public-health measures including tests and social distancing. He also asked them to resist bans on travel and trade because, historically, they had been of limited utility and are potentially harmful.

But governments around the world ignored those calls. For example, the United States did not roll out testing across the country until late February, and it banned some travel from China, where the virus was first discovered.

Countries seem to agree that to improve the world's ability to respond to pandemics, the WHO should be transformed and bolstered. Speaking as a representative of the United States, Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, told the WHO on 21 January that the country will reverse its withdrawal from the organization, initiated by former president Donald Trump, and will "work constructively with partners to strengthen and importantly reform the WHO".

"The real question is, what would it take for people to do something when a declaration happens?"

One change to strengthen the WHO could be a new treaty on pandemics, proposed by the president of the European Council, Charles Michel. On 20 January, Tedros said he would assemble a working group to explore this p. Still, the WHO probably wouldn't have the ability to penalize countries that don't comply with the treaty. "There's no silver bullet here since you're dealing with a community of nations, all of whom guard their sovereignty very closely," says Steven Solomon, principal legal officer at the WHO.

The WHO therefore relies on diplomacy, which often boils down to praising or shaming countries. But the WHO's appetite for criticism is limited by its reliance on donations from its member countries and on countries openly offering access and information — which could be withheld if leaders felt insulted. A case in point is that the WHO spent weeks gently persuading China to permit an international team of scientists to visit Wuhan after the outbreak was reported there. On the financing front, researchers say that a larger, reliable budget for the WHO would give the organization greater autonomy because it wouldn't be dependent on fundraising amid a disaster.

To address communication concerns, Tedros has suggested adding a gradient of warnings to the PHEIC, coded by colour. The colours could separate emergencies that might evolve into a pandemic from those that are serious but won't affect nations across the globe. Countries with outbreaks might more willingly share information if there were a low-grade alarm that was less likely to result in disruptions to people's livelihoods or the economy.

Reforms won't come until the World Health Assembly in May — at the earliest. The possibility of solutions being delayed or forgotten fills Liu with dread, because she recalls dozens of panels assessing failures in the response to the Ebola outbreak in West Africa in 2014–16. "Less than 10% of the recommendations were followed up on," she says. "We have an amazing talent to outrage ourselves about a situation, but when it comes time to deliver any change, there is very little traction, and people go back to doing whatever they had done before."

FAST-SPREADING COVID VARIANT CAN ELUDE IMMUNE RESPONSES

Early studies find that a variant of the virus identified in South Africa could compromise immunity.

By Ewen Callaway

Evidence is growing that some coronavirus variants could evade immune responses triggered by vaccines and previous infections. Researchers are trying to make sense of a tsunami of laboratory studies released last week that raise concerns about some emerging variants and mutations.

"Some of the data I've seen have really scared me," says Daniel Altmann, an immunologist at Imperial College London, who worries that some of the results could portend a reduction in the effectiveness of COVID-19 vaccines.

But the picture is murky, Altmann and other scientists emphasize. The studies — which examined the blood of small numbers of people who had recovered from COVID-19 or received a vaccine — probed only their antibodies' capacity to 'neutralize' variants in laboratory tests, and not the wider effects of other components of their immune response.

Neither do the studies indicate whether the changes in antibody activity make any difference to the real-world effectiveness of

© 2021 Springer Nature Limited. All rights reserved.

vaccines or the likelihood of reinfection. "Are these changes going to be important? I really don't know," says Paul Bieniasz, a virologist at the Rockefeller University in New York City, who co-led one of the studies.

Impacts on immunity

Much of the concern centres around a variant that researchers identified in South Africa in late 2020. A team led by Tulio de Oliveira, a bioinformatician at the University of KwaZulu-Natal in Durban, South Africa, linked the variant — called 501Y.V2 — to a fast-growing epidemic in Eastern Cape province that has since spread across South Africa and into other countries[1]. The lineage carries many mutations in the SARS-CoV-2 spike protein — the immune system's prime target, which allows the virus to identify and infect host cells — including some changes linked to weakened antibody activity against the virus.

The Eastern Cape was hit hard by South Africa's first COVID-19 wave, and researchers wondered whether the rapid spread of 501Y.V2 could be partly explained by its ability to elude previously established immune responses.

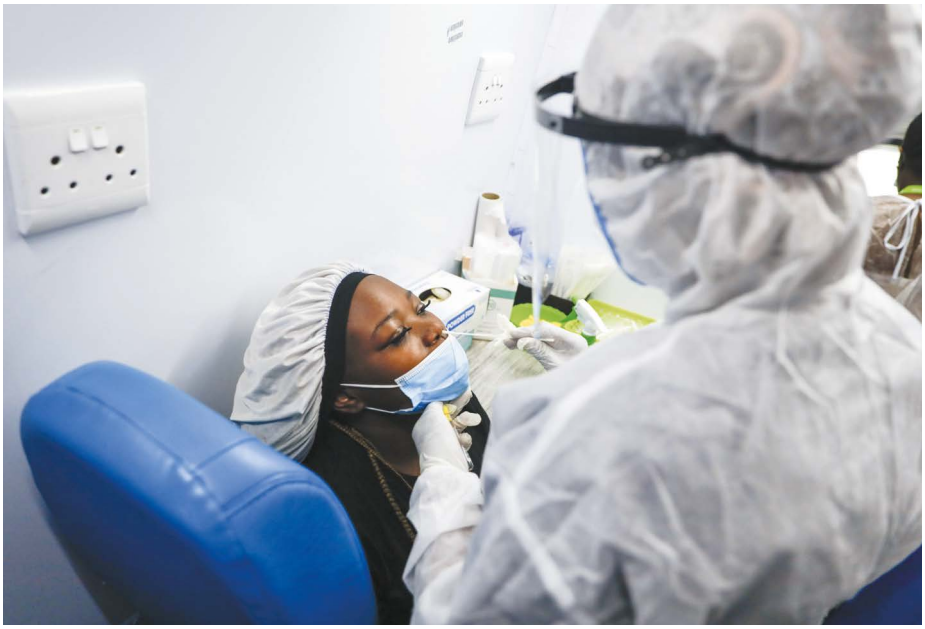
To investigate this, de Oliveira, virologist Alex Sigal at the Africa Health Research Institute in Durban and other colleagues isolated 501Y.V2 viruses from people infected with the variant[2]. They then tested the variant samples against serum — the antibody-containing portion of blood — taken from six people who had recovered from COVID-19 caused by other versions of the virus. This convalescent serum tends to contain neutralizing, or virus-blocking, antibodies that can prevent infection. The researchers found that the convalescent serum was much worse at neutralizing 501Y.V2 than at neutralizing variants that circulated earlier in the pandemic. Some people's plasma performed better against 501Y.V2 than did plasma from others, but in all cases, the neutralizing power was substantially weakened, says de Oliveira. "It's extremely worrying."

In a separate study[3], a team led by virologist Penny Moore at the National Institute for Communicable Diseases and the University of the Witwatersrand in Johannesburg, South Africa, probed the effects of convalescent serum on various combinations of spike mutations found in 501Y.V2. The researchers did this using a 'pseudovirus' — a modified form of HIV that infects cells using the SARS-CoV-2 spike protein.

These experiments showed that 501Y.V2 contains mutations that blunt the effects of neutralizing antibodies that recognize two key regions of spike: its receptor-binding and N-terminal domains. Pseudoviruses with the full package of 501Y.V2 mutations were fully resistant to convalescent serum from 21 out of 44 participants, and were partly resistant to the vast majority of people's sera.

Both South African teams will soon test the 501Y.V2 variant with serum from people who participated in COVID-19 vaccine trials, and similar studies are under way at labs worldwide. A team co-led by Bieniasz found that mutations in the receptor-binding domain of 501Y.V2 caused only a modest drop in the potency of antibodies from people who had received either the Pfizer or Moderna mRNA vaccines[4]. That's "a reassuring finding", says Moore, but it will be important to test the consequences of other mutations in 501Y.V2.

Whether these could lessen the effectiveness of vaccines is still uncertain, says Volker Thiel, an RNA virologist at the University of Bern in Switzerland. Most COVID-19 vaccines elicit high levels of antibodies that target diverse regions of the spike protein, so some of the molecules are likely to be able to block viral variants. And other components of the immune response, such as T cells, might not be affected by 501Y.V2.



GUILLEM SARTORIO/BLOOMBERG/GETTY

A coronavirus testing centre in South Africa, where the 501Y.V2 variant was detected in 2020.

> **"The whole idea of herd immunity would become a pipe dream."**

"Although the vaccines target only the spike gene, they should still mount an immune response that is diverse enough that these new variants should be covered," Thiel says. "But experimental studies need to be done."

A dampened antibody response to variants such as 501Y.V2 might not be much of a problem in practice, says Marion Koopmans, a virologist at the Erasmus Medical Centre in Rotterdam, the Netherlands. "You can see some change in a lab assay, which does not have an effect in a person because that person still has enough antibodies to neutralize the infection." It can also be difficult to disentangle whether reinfections are due to waning immune responses from the first infection, or to the effects of a mutation, she adds.

Emerging data

Clues are also beginning to emerge about the behaviour of a fast-spreading variant identified in the United Kingdom, known as B.1.1.7. In pseudovirus experiments, researchers at biotech firm BioNTech in Mainz, Germany, found that B.1.1.7's spike mutations had little effect on sera from 16 people who had received the vaccine the company developed with Pfizer[5]. Meanwhile, a team led by virologist Ravindra Gupta at the University of Cambridge, UK, looked at the sera of 15 people who had received the first of two doses of the same immunization[6]; the team found that 10 people's sera was less effective against B.1.1.7 than against other versions of SARS-CoV-2. These changes shouldn't make a difference to the vaccine's effectiveness now, says Gupta, but they could as antibody levels wane over time.

What last week's results mean for battling the pandemic are not yet clear. It is a top priority for researchers to determine whether mutations in 501Y.V2 are responsible for reinfections. If they are, says de Oliveira, "the whole idea of herd immunity would become a pipe dream, at least from natural infection".

1. Tegally, H. *et al*. Preprint at medRxiv https://doi.org/10.1101/2020.12.21.20248640 (2020).
2. Cele, S. *et al*. Preprint at https://www.ahri.org/wp-content/uploads/2021/01/MEDRXIV-2021-250224v1-Sigal.pdf (2021).
3. Wibmer, C. W. *et al*. Preprint at bioRxiv https://doi.org/10.1101/2021.01.18.427166 (2021).
4. Wang, Z. *et al*. Preprint at bioRxiv https://doi.org/10.1101/2021.01.15.426911 (2021).
5. Muik, A. *et al*. Preprint at bioRxiv https://doi.org/10.1101/2021.01.18.426984 (2021).
6. Collier, D. A. *et al*. Preprint at medRxiv https://doi.org/10.1101/2021.01.19.21249840 (2021).

© 2021 Springer Nature Limited. All rights reserved.