News in focus

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A hospital worker monitors a person with COVID-19 in South Africa, where a new variant of SARS-CoV-2 has been identified.

COULD NEW COVID VARIANTS UNDERMINE VACCINES? LABS SCRAMBLE TO FIND OUT

Researchers race to determine why lineages identified in Britain and South Africa spread so quickly, and whether vaccines will be less effective against them.

By Ewen Callaway

As concern grows over fast-spreading variants of the coronavirus SARS-CoV-2, laboratories worldwide are racing to unpick the biology of these viruses. Scientists want to understand why variants identified in the United Kingdom and South Africa seem to be spreading so quickly, and whether they might diminish the potency of vaccines or overcome natural immunity and lead to a spate of reinfections.

"Many of us are scrambling to make sense of the new variants, and the million-dollar question is what significance this will have for the effectiveness of vaccines that are currently being administered," says Jeremy Luban, a virologist at the University of Massachusetts Medical School in Worcester.

The first lab results are trickling in, as researchers rush to probe the variants and their mutations in cell and animal models of SARS-CoV-2, and test them against antibodies. A preprint published on 7 January[1] found that a mutation shared by both variants did not alter the activity of antibodies produced by people who received a vaccine developed by Pfizer and BioNTech. Data on other mutations and vaccines are expected soon.

Underlying biology

Researchers spotted the coronavirus variants in late November and early December 2020, through genome sequencing. A UK genomics effort determined that a virus variant now known as B.1.1.7 had been behind surging case

numbers in southeast England and London; the variant has now been detected in tens of countries worldwide (see 'Viral sequences').

And a team led by bioinformatician Tulio de Oliveira at the University of KwaZulu-Natal in Durban, South Africa, connected[2] a fast-growing epidemic in the country's Eastern Cape Province to a variant that the researchers call 501Y.V2. The two variants emerged independently, but both carry a bevy of mutations – some of them similar – in the spike protein, through which the coronavirus identifies and infects host cells, and which serves as the chief target of the human immune response.

Epidemiologists studying the spread of the B.1.1.7 variant have estimated that it is around 50% more transmissible than other variants of SARS-CoV-2 known to be in circulation[3] – an insight that contributed to the UK government's decision to enter a further national lockdown. "The epidemiology has really shown us the way here," says Wendy Barclay, a virologist at Imperial College London and a member of a group advising the government on its response to B.1.1.7. But it is important, Barclay adds, that scientists determine the underlying biology. "Understanding what properties of the virus make it more transmissible allows us to be more informed about policy decisions."

Family resemblance

One challenge is disentangling the effects of the mutations that distinguish the lineages from their close relatives. The B.1.1.7 variant carries eight changes that affect the spike protein, and several more in other genes; samples of the 501Y.V2 variant carry up to nine changes to the spike protein. Working out which are responsible for the rapid spread of the variants and their other properties is an "enormous challenge", says Luban. "I don't think there's a single mutation that's accounting for all of it."

Much of the effort is focused on a change to the spike protein that is present in both lineages, called N501Y. This mutation alters a portion of the spike, called the receptor binding domain, that locks onto a human protein to allow infection. Previous studies have hinted that the N501Y change allows the virus to attach to cells more strongly, making infection easier, says Barclay.

A team led by Vineet Menachery, a virologist at the University of Texas Medical Branch (UTMB) in Galveston, is preparing to examine N501Y and other mutations in hamsters, which are models for studying SARS-CoV-2 transmission. Menachery was part of a team that reported[4] last year that a different mutation to the spike protein enabled viruses to reach greater concentrations in hamsters' upper airways, compared with viruses lacking the change. "That's what I'm expecting with these mutations," he says. "If that's the case, that's going to be driving their transmissibility."

The rapid spread of the variants has triggered efforts to contain them, such as lockdowns. Adding to the sense of urgency is the worry that the variants could weaken immune responses initiated by vaccines and previous infection. Both variants harbour mutations in regions of the spike protein that are recognized by potent 'neutralizing', or virus-blocking, antibodies, says Jason McLellan, a structural biologist at the University of Texas at Austin, who studies coronavirus spike proteins. This raises the possibility that antibodies to these regions – the receptor binding domain and a portion called the N-terminal domain – could be affected by the mutations.

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As a result, academic and government researchers and vaccine developers are now working to address the question. "This is crazy speed," says Pei-Yong Shi, a virologist at UTMB who is collaborating with Pfizer to analyse blood from participants in the company's successful vaccine trial. In the 7 January preprint[1], the team found that antibodies generated by 20 participants with viruses carrying the N501Y mutation were roughly as potent as antibodies produced to combat viruses lacking the change.

Immune escape

But other mutations might affect immunity. Chief among those is a receptor-binding-domain mutation called E484K, which de Oliveira's team has identified in the 501Y.V2 variant. The team is testing whether the variant is affected by antibodies in blood serum from people who have recovered from coronavirus infection, and from vaccine-trial participants.

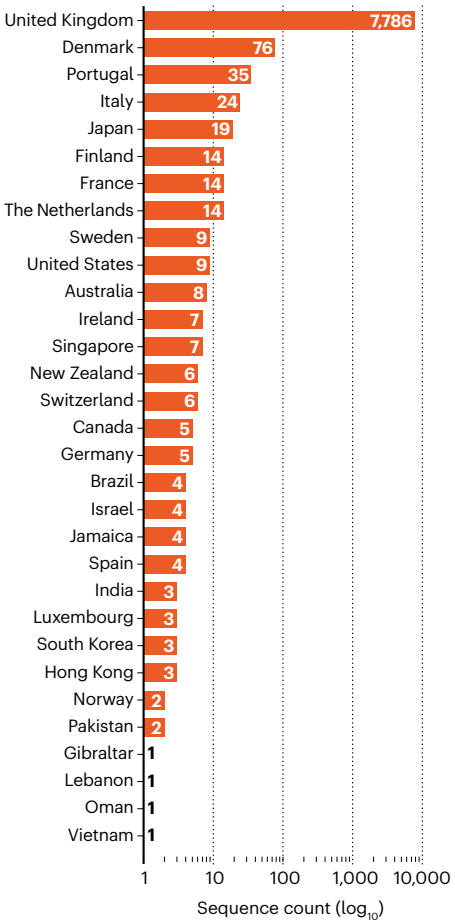
There is emerging evidence that the E484K mutation can enable the virus to escape some people's immune responses. In a 28 December preprint[5], researchers grew SARS-CoV-2 in the presence of low levels of one person's convalescent serum. The goal was to select for viral mutations that evade the diverse repertoire of antibodies generated in response to infection. "The experiment wasn't necessarily supposed to work," says McLellan, a co-author. But within 90 days, the virus had picked up 3 mutations that made it impervious to the person's serum. One was the E484K mutation; the others were N-terminal domain changes found in the South African and the UK variant. "That was surprising," says McLellan, because it suggested that the individual's entire antibody response against SARS-CoV-2 was directed against a small portion of the spike protein.

A pressing question is whether such changes will alter the real-world effectiveness of vaccines, says Jesse Bloom, a viral evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington. And, in a 4 January preprint[6], his team reported that E484K and several other mutations can escape recognition by antibodies in convalescent sera to varying degrees.

But Bloom and other scientists are hopeful that the mutations in the variants won't substantially weaken the performance of vaccines. The shots tend to elicit whopping levels of neutralizing antibodies, so a small drop in their potency against the variants might not matter. "If I had to bet right now, I would say the vaccines are going to remain effective for the things that really count – keeping people from getting deathly ill," says Luban.

VIRAL SEQUENCES

Genome-sequencing efforts are crucial to understanding how the SARS-CoV-2 coronavirus is mutating. A fast-spreading variant, called B.1.1.7, was identified by a UK-wide COVID-19 genomics effort, and 31 countries or regions have now uploaded sequence data to the GISAID website.



SOURCE: DATA FROM GISAID/ANGIE HINRICHS, UNIV. CALIFORNIA, SANTA CRUZ, GENOMICS INST.; DATA AS OF 6 JANUARY 2021

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