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IN DEPTH



Relatives attend
a COVID-19
victim's burial in
Manaus, Brazil,
on 13 January.

COVID-19

New mutations raise specter of 'immune escape'

SARS-CoV-2 variants found in Brazil and South Africa may evade human antibodies

By Kai Kupferschmidt

When the number of COVID-19 cases began to rise again in Manaus, Brazil, in December 2020, Nuno Faria was stunned. The virologist at Imperial College London had just co-authored a paper in *Science* estimating that three-quarters of the city's inhabitants had already been infected with SARS-CoV-2, the pandemic coronavirus—more than enough, it seemed, for herd immunity to develop. The virus should be done with Manaus. Yet hospitals were filling up again. "It was hard to reconcile these two things," Faria says. He started to hunt for samples he could sequence to find out whether changes in the virus could explain the resurgence.

On 12 January, Faria and his colleagues posted their initial conclusions on the website virological.org. Thirteen of 31 samples collected in mid-December in Manaus turned out to be part of a new viral lineage they called P.1. Much more research is needed, but they say one possibility is that in some people, P.1 eludes the human immune response

triggered by the lineage that ravaged the city earlier in 2020.

Emerging variants of the coronavirus have been in the news ever since scientists raised the alarm over B.1.1.7, a SARS-CoV-2 variant that first caught scientists' attention in England in December and that is more transmissible than previously circulating viruses (*Science*, 8 January, p. 108). But now, they're also focusing on a potential new threat: variants that could do an end run around the human immune response. Such "immune escapes" could mean more people who have had COVID-19 remain susceptible to reinfection, and that proven vaccines may, at some point, need an update.

At a World Health Organization (WHO) meeting on 12 January, hundreds of researchers discussed the most important scientific questions raised by the wave of new mutations. WHO also convened its COVID-19 Emergency Committee on 14 January to discuss the impact of the new vari-

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ants and the travel restrictions that many countries are imposing to contain them. The committee called for a global effort to sequence more SARS-CoV-2 genomes to help track mutations.

The more transmissible variant, B.1.1.7, is already spreading rapidly in the United Kingdom, Ireland, and Denmark, and probably in many other countries. But scientists are just as worried about 501Y.V2, a variant detected in South Africa. Some of the mutations it carries, including ones named E484K and K417N, change its surface protein, spike, and have been shown in the lab to reduce how well monoclonal antibodies combat the virus. In a preprint published earlier this month, Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center, showed that E484K also reduced the potency of convalescent sera from some donors 10-fold—although he is quick to add this does not necessarily mean the mutation would cause people's immunity to the new strain to drop 10-fold.

P.1 adds to the concerns because it appears to have hit on a similar constellation of muta-

PHOTO: MICHAEL DANTAS/AFP/GETTY IMAGES

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tions and has emerged in a place with a high level of immunity. “Anytime you see the same mutations arising and starting to spread multiple times, in different viral strains across the world, that’s really strong evidence that there’s some evolutionary advantage to those mutations,” Bloom says.

Like B.1.1.7, the Brazilian variant is already on the move. Just as Faria was finishing his analysis of the Brazilian genomes, a report was published of a variant detected in travelers arriving in Japan from Brazil—and it turned out to be P.1. (As *Science* went to press, U.S. researchers also reported several new variants, but their importance remained unclear.)

HOW THESE NEW variants are affecting the course of the pandemic is unclear. In Manaus, for example, P.1 might have nothing to do with the new surge in infections; people’s immunity might simply be waning, says University of Oxford epidemiologist Oliver Pybus. Or it might be driving the boost because it is transmitted more easily, like B.1.1.7, not because it can evade the immune response. “Of course it could be a combination of these factors, too,” Pybus says.

Similarly, in a recent modeling study, researchers at the London School of Hygiene & Tropical Medicine calculated that South Africa’s 501Y.V2 variant could be 50% more transmissible but no better at evading immunity, or just as transmissible as previous variants but able to evade immunity in one in five people previously infected. “Reality may lie between these extremes,” the authors wrote.

Ester Sabino, a molecular biologist at the University of São Paulo, São Paulo, has launched a study to find reinfections in Manaus that could help decide between these hypotheses for P.1. Lab studies investigating the variants are also underway. The United Kingdom on 15 January launched a new consortium, G2P-UK (for “genotype to phenotype-UK”), headed by Wendy Barclay of Imperial College London, to study the effects of emerging mutations in SARS-CoV-2. One idea discussed at the 12 January WHO meeting is to set up a biobank that would aid studies by housing virus samples, as well as plasma from vaccine recipients and recovered patients.

Interactions between the new mutations may make it harder to tease out their effects. The variants from the United Kingdom, South Africa, and Manaus all share a mutation named N501Y, for instance, or Nelly, as some researchers call it. But the mutation, which

affects the spike protein, also occurs in some variants that do not spread faster, suggesting N501Y does not operate alone, says Kristian Andersen of Scripps Research: “Nelly might be innocent, except maybe when she’s hanging with her bad friends.”

Bloom thinks none of the changes is likely to let the virus escape the immune response entirely. “But I would expect that those viruses have some advantage when a lot of the population has immunity”—which might help explain the surge in Manaus.

SO FAR THE VIRUS does not appear to have become resistant to COVID-19 vaccines, says vaccinologist Philip Krause, who chairs a WHO working group on COVID-19 vaccines. “The not-so-good news is that the rapid evolution of these variants suggests that if it is possible for the virus to evolve into a vaccine-resistant phenotype, this may happen sooner than we like,” he adds. That



People line up to receive a COVID-19 vaccine in Birmingham, U.K.

possibility adds to the urgency of putting good surveillance in place to detect such escape variants early on, says biostatistician Natalie Dean of the University of Florida.

Some scientists worry that proposed changes in vaccine dosing regimens could hasten the evolution of such strains. Desperate to tame a massive surge in cases, the United Kingdom on 30 December decided to allow up to 12 weeks between the first and second dose of two authorized vaccines, rather than the 3 or 4 weeks used in the vaccines’ clinical trials, so more people can get their first dose quickly and have at least some immunity. And the Trump administration decided to ship all available doses immediately, rather than holding back 50% to guarantee that people receive their second doses on time. That policy, which the Biden administration has said it will follow, could inadvertently extend the

dosing interval if future vaccine deliveries don’t arrive or aren’t administered on time.

Widespread delays of the second dose might create a pool of millions of people with enough antibodies to slow the virus and avoid getting sick, but not enough to wipe it out. That could well be the perfect recipe for creating vaccine-resistant strains, says virologist Florian Krammer of the Icahn School of Medicine at Mount Sinai: “If we end up with everybody just getting one dose with no doses available for a timely boost, that would in my opinion, be a problem.”

But others say unchecked spread of the virus poses greater risks. “It’s carnage out there,” says evolutionary microbiologist Andrew Read of Pennsylvania State University, University Park. “Twice as many people with partial immunity has got to be better than full immunity in half of them.”

Historically, few viruses have managed to evolve resistance to vaccines, with the notable exception of seasonal influenza, which evolves so rapidly on its own—without vaccine pressure—that it requires a newly designed vaccine every year.

If vaccine-resistant SARS-CoV-2 strains emerge, vaccines might need to be updated. Several vaccines could be easily changed to reflect the latest changes, but regulators might balk at authorizing them without seeing updated safety and efficacy data, Krause says. If new variants circulate alongside older strains, multivalent vaccines, effective against several lineages, might even be needed. “To be clear: These are downstream considerations,” Krause says. “The public should not think that this is imminent, and that new vaccines will be needed.”

But Ravindra Gupta, a researcher at the University of Cambridge, says manufacturers should start to produce vaccines designed to generate immunity to mutated versions of the spike protein, because they keep cropping up. “It tells us that we should have these mutations in our vaccines, so that you shut off one of the avenues for the virus to go down.”

For now, increased transmissibility is the biggest worry, says virologist Angela Rasmussen of Georgetown University. “I’m puzzled why [that] isn’t a bigger part of the conversation,” she says. The U.S. hospital system, she says, “is at capacity in many places and further increases in transmission can tip us over the edge where the system collapses. Then we’ll start seeing potentially huge increases in mortality.” ■

With reporting by Meredith Wadman.