Shoppers wear face masks on Regent Street in London on 19 December, the day the U.K. government imposed new restrictions to curb a rapidly spreading new SARS-CoV-2 variant. AP PHOTO/ALBERTO PEZZALI

U.K. variant puts spotlight on immunocompromised patients' role in the COVID-19 pandemic

By **Kai Kupferschmidt** | Dec. 23, 2020 , 2:30 PM

***Science*'s COVID-19 reporting is supported by the Pulitzer Center and the Heising-Simons Foundation.**

In June, Ravindra Gupta, a virologist at the University of Cambridge, heard about a cancer patient who had come into a local hospital the month before with COVID-19 and was still shedding virus. The patient was being treated for a lymphoma that had relapsed and had been given rituximab, a drug that depletes antibody-producing B cells. That made it hard for him to shake the infection with SARS-CoV-2.

Gupta, who studies how resistance to HIV drugs arises, became interested in the case and helped treat the patient, who died in August, 101 days after his COVID-19 diagnosis, despite being given the antiviral drug remdesivir and two rounds of plasma from recovered patients, which contained antibodies against the virus. When Gupta studied genome sequences from the coronavirus that infected the patient, he discovered that SARS-CoV-2 had acquired several mutations that might have allowed it to elude the antibodies.

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immunocompromised patient who had a long-running infection. "It's a perfectly logical and rational hypothesis," says infectious disease scientist Jeremy Farrar, director of the Wellcome Trust.

Scientists are still trying to figure out the effects of the mutations in B.1.1.7, whose emergence led the U.K. government to tighten coronavirus control measures and other countries in Europe to impose U.K. travel bans. But the new variant, along with research by Gupta and others, has also drawn attention to the potential role in COVID-19 of people with weakened immune systems. If they provide the virus with an opportunity to evolve lineages that spread faster, are more pathogenic, or elude vaccines, these chronic infections are not just dangerous for the patients, but might have the potential to alter the course of the pandemic.

It's still very unclear whether that is the case, but Farrar believes it's important to ensure doctors take extra precautions when caring for such people: "Until we know for sure, I think, treating those patients under pretty controlled conditions, as we would somebody who has drug resistant tuberculosis, actually makes sense."

Researchers' concern mostly focuses on cancer patients being treated for chemotherapy and similar situations. "We don't yet know about people who are immunocompromised because of HIV, for instance," Farrar says.

Foreshadowing the future

B.1.1.7 attracted scientists' attention because it was linked to an outbreak in England's Kent county that was growing faster than usual. Sequences showed that virus had accumulated a slew of mutations that together caused 17 amino acid changes in the virus' proteins, eight of them in the crucial spike protein. Among them are at least three particularly concerning ones.

One is 69-70del, a deletion that Gupta also found in his Cambridge, U.K., patient whose virus seemed to evade the immune system. It leads to the loss of two amino acids in the spike protein. In lab experiments, Gupta found that lentivirus engineered to carry the SARS-CoV-2 spike protein with this deletion was twice as infectious.

The second is N501Y, a mutation that evolutionary biologist Jesse Bloom of the Fred Hutchinson Cancer Research Center has shown to increase how tightly the protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor, its entry point into human cells. The mutation is also present in 501Y.V2, a variant discovered by researchers in South Africa who investigated rapidly growing outbreaks in three coastal provinces. "We found that this lineage seems to be spreading much faster," says Tulio de Oliveira, a virologist at the University of KwaZulu-Natal whose work first alerted U.K. scientists to the importance of N501Y. "Anytime you see the same mutation being independently selected multiple times, it increases the weight of evidence that that mutation is probably beneficial in some way for the virus," Bloom says.

The third worrisome change is P681H, which alters the site where the spike protein has to be cleaved to enter human cells. It is one of the sites on spike where SARS-CoV-2 differs from SARS-CoV-1, the virus that caused the worldwide outbreak of severe acute respiratory syndrome in 2003, and the change there may allow it to spread more easily. "This one is probably as important as N501Y," says Christian Drosten, a virologist at Charité University Hospital in Berlin.

So far, SARS-CoV-2 typically acquires only one to two mutations per month. And B.1.1.7 is back to this pace now, suggesting it doesn't mutate faster normally than other lineages. That's why scientists believe it may have gone through a lengthy bout of evolution in a chronically infected patient who then transmitted the virus late in their infection. "We know this is rare but it can happen," says World Health Organization epidemiologist Maria Van Kerkhove. Stephen Goldstein, a virologist at the University of Utah, agrees. "It's simply too many mutations to have accumulated under normal evolutionary circumstances. It suggests an extended period of within-host evolution," he says.

People with a weakened immune system may give the virus this opportunity, as Gupta's data show. More evidence comes from a paper published in *The New England Journal of Medicine* on 3 December that described an immunocompromised patient in Boston infected with SARS-CoV-2 for 154 days before he died. Again, the researchers found several mutations, including N501Y. "It suggests that you can get relatively large numbers of mutations happening over a relatively short period of time within an individual patient," says William Hanage of the Harvard T.H. Chan School of Public Health, one of the authors. (In patients who are infected for a few days and then clear the virus, there simply is not enough time for this, he says.) When such patients are given antibody treatments for COVID-19 late in their disease course, there may already be so many variants present that one of them is resistant, Goldstein says.

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> *Stephen Goldstein, University of Utah*

The question is whether the mutations arising in such patients could also help the virus spread more rapidly. In **research published a few years ago**, Bloom showed some of the mutations that arose in influenza viruses in immunocompromised patients later spread globally. "It's totally possible that what's happening in immunocompromised patients could foreshadow what happens in the future" with the pandemic, Bloom says. But adaptations that help a virus outperform other viruses in a patient can also be very different from what a virus needs to better transmit from patient to patient, he says.

like there is something to do with this variant." Drosten says he was initially skeptical, but has become more convinced as well.

But exactly what impact each mutation has is much more difficult to assess than spotting them or showing they're on the rise, says Seema Lakdawala, a biologist at the University of Pittsburgh. Animal experiments can help show an effect, but they have limitations. Hamsters already transmit SARS-CoV-2 virus rapidly, for instance, which could obscure any effect of the new variant. Ferrets transmit it less efficiently, so a difference may be more easily detectable, Lakdawala says. "But does that really translate to humans? I doubt it." A definitive answer may be months off, she predicts.

One hypothesis that scientists are discussing is that the virus has increased how strongly it binds to the ACE2 receptor on human cells, and that this allows it to better infect children than before, expanding its playing field. But the evidence for that is very thin so far, Çevik says. Even if children turn out to make up a higher proportion of people infected with the new variant, that could be because the variant spread at a time when there was a lockdown but schools were open. Another hypothesis is that P681H helps the virus better infect cells higher up in the respiratory tract, from where it can spread more easily than from deep in the lungs, Drosten says.

No reason to freak out

One important question is whether the South African or U.K. lineage might lead to more severe disease or even evade vaccine-induced immunity. So far there is little reason to think so. Although some mutations have been shown to let the virus evade monoclonal antibodies, vaccines and natural infections both appear to lead to a broad immune response that targets many parts of the virus, says Shane Crotty of the La Jolla Institute for Immunology. "It would be a real challenge for a virus to escape from that." The measles and polio viruses have never learned to escape the vaccines targeting them, he notes: "Those are historical examples suggesting not to freak out."

At a press conference yesterday, BioNTech CEO Uğur Şahin pointed out that the U.K. variant differed in only nine out of more than 1270 amino acids of the spike protein encoded by the messenger RNA in the very effective COVID-19 vaccine his company developed together with Pfizer. "Scientifically it is highly likely that the immune response by this vaccine also can deal with the new virus," he said. Experiments are underway that should confirm that in the first week of 2021, Şahin added.

Sébastien Calvignac-Spencer, an evolutionary virologist at the Robert Koch Institute, says this marks the first time countries have taken such drastic actions as the U.K. lockdown and the travel bans based on genomic surveillance in combination with epidemiological data. "It's pretty unprecedented at this scale," he says. But the question of how to react to disconcerting mutations in pathogens will crop up more often as genomic surveillance expands, he predicts. People are happy they prepared for a category 4 hurricane even if predictions turn out to be wrong and the storm is less severe, Calvignac-Spencer says. "This is a bit the same, except that we have much less experience with genomic surveillance than we have with the weather forecast."

Although the rise of B.1.1.7 in the United Kingdom is troubling, Farrar says he is equally concerned about the other variant spreading quickly in South Africa and that has now been detected in two travelers in the United Kingdom as well. It includes two further mutations in the part of the spike protein that binds to its receptor on human cells, K417N and E484K. These could impact the binding of the virus to human cells and also its recognition by the immune system, Farrar says. "These South African mutations I think are more worrying than the constellation of the British variant." South African hospitals are already struggling, he adds. "We've always asked, 'Why has sub-Saharan Africa escaped the pandemic to date?" Answers have focused on the relative youth of the population and the climate. "Maybe if you just increase transmission a bit, that is enough to get over these factors," Farrar says.

To Van Kerkhove, the arrival of B.1.1.7 shows how important it is to follow viral evolution closely. The United Kingdom has one of the most elaborate monitoring systems in the world, she says. "My worry is: How much of this is happening globally, where we don't have sequencing capacity?" Other countries should beef up their efforts, she says. And all countries should do what they can to minimize transmission of SARS-CoV-2 in the months ahead, Van Kerkhove says. "The more of this virus circulates, the more opportunity it will have to change," she says. "We're playing a very dangerous game here."

Posted in: **Health**, **Coronavirus**
doi:10.1126/science.abg2911

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