SCIENCE

The Coronavirus's Next Move

Here are four shapes that the next variant might take—which will also dictate the shape of our response.

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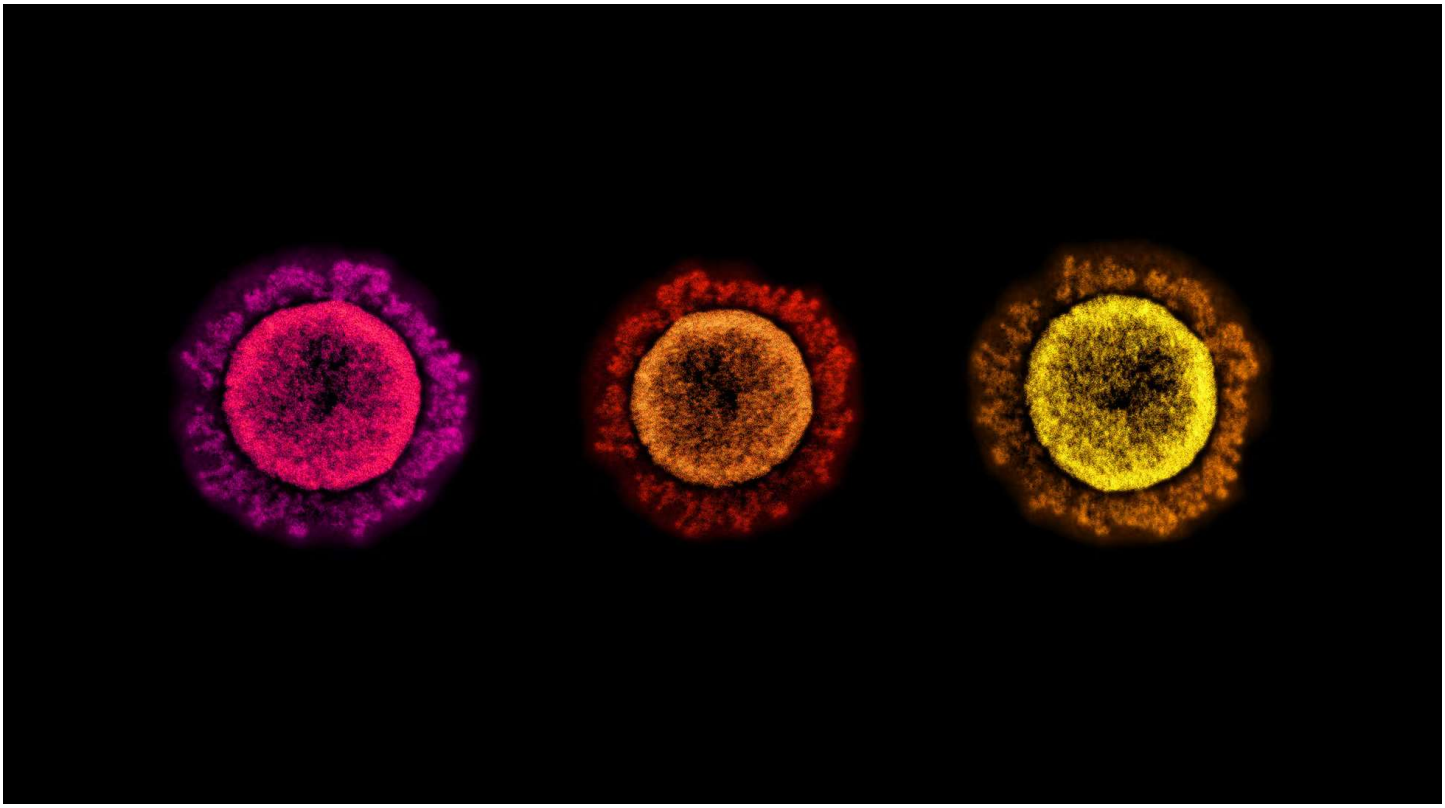

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If the coronavirus has one singular goal—repeatedly infecting us—it's only gotten better at realizing it, from Alpha to Delta to Omicron. And it is nowhere near done. "Omicron is not the worst thing we could have imagined," says Jemma Geoghegan, an evolutionary virologist at the University of Otago, in New Zealand. Somewhere out there, a Rho, a Tau, or maybe even an Omega is already in the works.

Not all variants, though, are built the same. The next one to trouble us could be like Delta, speedy and a shade more severe yet still trounceable with existing vaccines. It could riff on Omicron's motif, eluding the defenses raised by infections and shots to an extent we've not yet seen. It could merge the worst aspects of *both* of those predecessors, or find its own successful combo of traits. Each iteration of the virus will require a slightly different set of strategies to wrangle it—the ideal approach will depend on "how sick are people getting, and which people are getting sick," Angela Shen, a vaccine-policy expert at Children's Hospital of Philadelphia, told me.

Our actual response won't just depend on the mix of mutations that the virus lobs our way. It will also hinge on how seriously we take those changes, and what state the virus finds us in when it slams us—immunologically, psychologically. While the next spotlight-hogging variant is still brewing, we can sketch out, in broad and not-at-all-comprehensive strokes, a subset of the cast of characters that could arise, and what it would take to fend off each one.

The Sharpshooter

Let's start with the worst-case scenario, because it's also probably the least likely. A new variant checks each of the Big Three boxes: more transmissible, more deadly, and much more evasive of the defenses that vaccines and other SARS-CoV-2 flavors have laid down.

In this version of events, even immunized people could suffer high rates of severe disease; additional boosters might not mount a sufficient blockade. The chasm in protection between the vaccinated and unvaccinated would start to close—perhaps rapidly, if the new variant collides with us when many people aren't up-to-date on their shots and population immunity is low.

Such a virus might be so strange-looking that some of our tests and many of our antibody-based treatments could stop working. Viral spread would also outpace what diagnostic tools we have left, obliterating contact-tracing efforts and making the pathogen harder to cordon off. Hundreds of thousands of people in the United States alone could lose their lives in a matter of months, as one recent analysis noted. Countless more would be hospitalized or saddled with the debilitating symptoms of long COVID. This future would feel most like the past—a near-reversion to "the first year of the pandemic," Crystal Watson, a senior associate at the Johns Hopkins Center for Health Security, told me. And, accordingly, this future would launch the most dramatic response.

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First, we'd have to start cooking up a new vaccine, tailored to fit a sniper-style variant's quirks. That alone would take at least three months, by shot-makers' current best estimates, not counting the arduous process of rolling out the updated vaccine quickly and equitably. In the interim, if we wanted to avoid the worst impacts, we'd have to lean heavily on our old standbys: high-quality masks, potentially mandated into use; restricted travel; capacity limits at—possibly even brief closures of—restaurants, bars, and gyms. (Hopefully, by this point, good ventilation and air filtration would be more widespread too.) The government might need to fund efforts to develop and distribute new tests and treatments. If the outbreak couldn't be contained, essential spaces such as schools might consider shutting their doors again—though Natalie Quillian, the deputy coordinator of the White House's COVID-19 response team,

told me that, from the standpoint of the administration, "we really don't see a scenario where schools need to close."

Thankfully, a variant quite this bad would be hard to come by. Viruses can't rejigger their genomes infinitely—not if they want to keep efficiently infecting their preferred hosts. Vineet Menachery, a virologist at the University of Texas Medical Branch, thinks the virus will probably chance upon ways to dodge immunity to a greater degree than Omicron did. But, he added, "the question is, does it have to give up something else to do that?"

Even if the virus remakes itself many times, we can expect that its offense will still knock up against some multilayered defenses. Slipping out of the grasp of antibodies isn't that hard, but "just statistically speaking, I don't think it's possible to escape T-cell immunity," says John Wherry, an immunologist at the University of Pennsylvania, a contributor to a recent report that modeled various scenarios for our future with COVID. The trick, then, would be rousing enough public will to use those backstop tools and duel the virus again—not a sure thing if a doom-esque variant appears anytime soon. "The acceptability of policy X, Y, or Z is not going to be the same as it was before," Shen told me.

The Escape Artist and the Brute

The Escape Artist and the Brute

In a less catastrophic forecast, a variant wouldn't pose an epic triple threat. But it could still pummel a substantial fraction of the population by ratcheting up *one* trait at a time. That could be any of the Big Three, but consider two examples: a juice-up in immune evasion, or a surge in virulence. All else equal, each could spark waves of serious disease and push the health-care system back to a breaking point.

First, the evasive option. SARS-CoV-2 now faces huge pressure to find an immunological escape hatch. With so many people having been infected, vaccinated, or both, the coronavirus's success has started to lean heavily on its ability to sidestep our shields. This future could be an even more dramatic version of the recent Omicron wave: None of us, no matter how many shots we've gotten, would truly be impervious to infection, or maybe even to serious illness. Through sheer numbers alone, this variant would be poised to land a huge swath of people in the hospital, even if it wasn't, particle for particle, a more deadly threat. Depending on the extent to which the variant eroded vaccine effectiveness, especially against hospitalization and death, we might still need to update our shots and launch a massive revaccination campaign. From the view of the White House, a variant would have to "pass a fairly strong threshold to want to do that," Quillian told me. "It's a pretty extensive effort to go back and revaccinate the entire population."

In some ways, a more *virulent* variant that was still susceptible to vaccine-induced defenses could be simpler to deal with. We could expect that people who were up-to-date on their shots would be very well protected, as they were against, say, Delta. The focus would be on shielding the most vulnerable: the unvaccinated, the elderly, the immunocompromised, those with heavy or frequent exposures to the virus—all of whom would likely benefit from more vaccine doses, and additional focused measures around masking, distancing, testing, and treatments. And perhaps our responses would remain siloed in these groups. "It would probably take a while for us to reimpose restrictions on the general population," Watson, of Johns Hopkins, said.

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Maybe that's not surprising. If much of society remains swaddled in safety, many people won't see a point in reinvesting in vigilance. The suffering of the people who we are already cultured to see as sickly or close to death—or who are concentrated in already marginalized communities—can be easy to overlook. "If it's the elderly, the immunocompromised, unfortunately, I think we're not viewing them in the same light as we would if it was the whole population," Menachery, the UTMB virologist, said. Which groups ultimately end up shouldering the brunt of the virus's burden will dictate the extent of our response.

Perhaps more of us would be galvanized into camaraderie if a variant pulled a wild card and upped its virulence in an unexpected group. If young adults or children, for instance, suddenly became a prime target, "I have to believe the response would be different," says Tom Bollyky, the director of the global-health program at the Council on Foreign Relations, and a contributor to the report on future-COVID scenarios. (Menachery thinks a sudden downshift into kids would be unlikely—that's not a typical modus operandi for coronaviruses.)

The Sprinter

There's a third axis on which the virus could shift—sheer transmissibility. Some mutation, or combination of them, could make the virus a bit more efficient at

mutation, or combination of them, could make the virus a bit more efficient at zipping between bodies. But without an accompanying supercharge of virulence, or extreme immune evasion, "I'm not sure there'd be much of a response, to be honest with you," Watson said.

Some people *might* feel motivated to sign up for a booster. A few localities *might* push for masking again. Or not. And should a bump in spreadability team up with a drop in virulence, the public's reaction might be more muted still. People might get sick, but with immunity on our side, the *proportion* of cases that wind up in the hospital would also dwindle—a deceptively comforting statistic to see. "I have a hard time believing anyone's going to care, unless there's more severity," says Adam Lauring, a virologist at the University of Michigan. Perhaps we'd see this variant's annual hospitalization and death burden on par with or below the flu's, a level of suffering that Americans have already implicitly (and perhaps misguidedly) decided is fine.

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But souped-up transmissibility is an insidious parlor trick. It helps viruses catch entire populations off guard. Even a somewhat defanged variant can sow chaos if it's given the opportunity to spread far and wide enough, and find the vulnerable among us. And we'd still be in deep trouble if a fleet-footed variant hit us at a time when we'd let our vigilance over vaccination slip, or if efforts to dose up the world's population equitably were still lagging behind. Plenty of suffering can unfold outside of hospitals as well. Less-severe SARS-CoV-2 infections can still seed long COVID. Hours would still be lost to isolations and illnesses. And though population immunity might be higher than ever right *now*, protection isn't spread evenly: Too many Americans haven't gotten any shots at all, and many of those who have remain vulnerable because of their age or health conditions.

Even if, somehow, the virus were to become completely, truly benign, total complacency could be dangerous. A virus we let spread is a virus that suddenly has "more hosts in which to evolve," Geoghegan, the University of Otago virologist, told me. Among them might be immunocompromised individuals, who could harbor the virus long-term. It could tinker with its genome until, "by chance, it comes up with the perfect combo of mutations," she said, and then roar back into the population at large. Menachery also worries about SARS-CoV-2's penchant for stewing and shape-shifting in other animal species. That's what has the potential, he told me, to give us SARS-CoV-3—to spark the *next* coronavirus pandemic.

We can't say when the next threat will appear, or how formidable it will be. But we do have some control over its emergence: The more chances we give the virus to infect us, the more chances we give it to change itself again.