Decoding delta: How viruses mutate and what can be done about it

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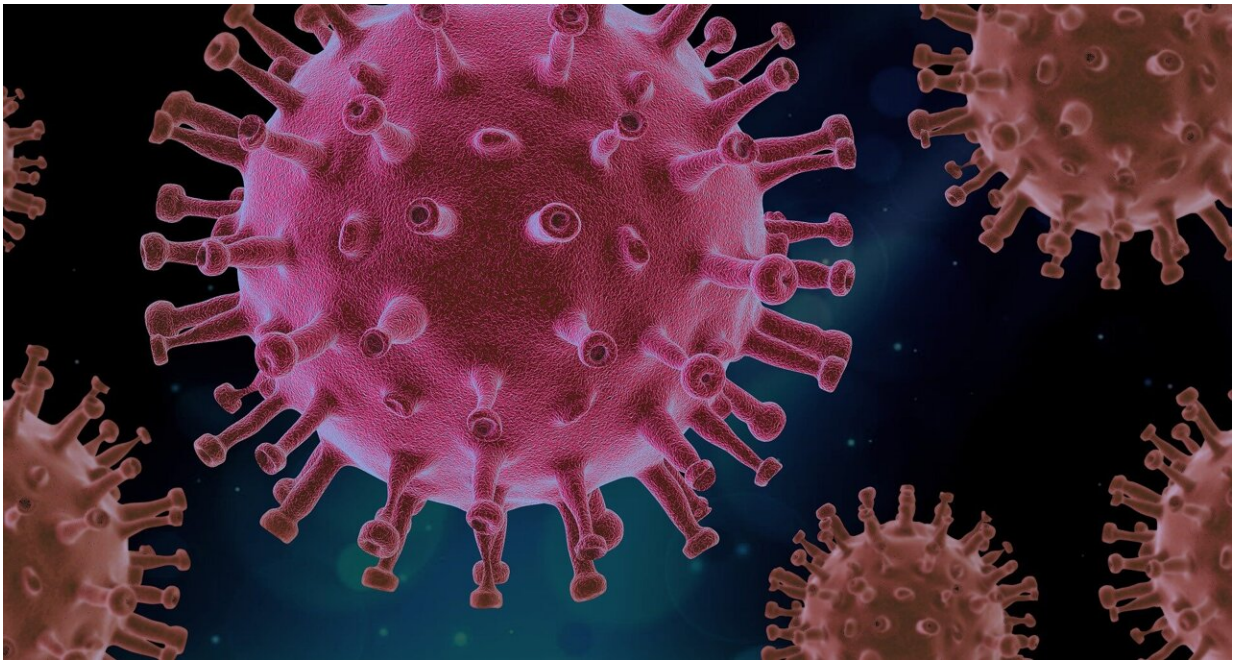

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Even as some Americans resume pre-pandemic activities like social gatherings or dining or shopping mask-free, a perilous schism is emerging in the U.S. between those who are vaccinated against COVID-19 and those who are not. And circulating almost exclusively among those who are unvaccinated is a potential threat to everyone: coronavirus variants.

U.S. cases of COVID-19 have more than doubled in the past two weeks, with the delta variant accounting for more than half of new infections, according to the Centers for Disease Control and Prevention. Virus variants themselves are not unexpected—viruses mutate frequently, and occasionally a new form provides enough viral advantages that it can take hold and spread throughout a community. But the rapidity with which new viral strains of SARS-CoV-2 are emerging suggests that the greatest tool in the public health arsenal now is vaccination, which would prevent infections—and further viral mutations—from occurring in the first place.

"Say, for example, it's a one in a million chance that a mutation will be advantageous to the virus. If you let the virus replicate itself 900,000 times, odds are that the advantageous mutation will occur," says Johns Hopkins virologist Andrew Pekosz. "But if you limit the overall replication of the virus to 1,000 times, then it's much less likely that the random advantageous mutation is going to occur. And that's where public health interventions really help us a lot during this pandemic—by reducing the total amount of virus replication and therefore reducing the chances that the virus can improve or adapt."

The Hub spoke with Pekosz for more insights into virus variants, how they emerge, and what can be done to prevent them.

What makes the delta variant different from the other strains of coronavirus currently circulating in the U.S.?

We have some ideas, but we don't know everything about what's changed with delta to make it more transmissible. We know that if we look at the spike protein, which is the protein the virus uses to attach to cells and start the infection process, we see that there are mutations that make that

protein better at entering human cells. We can also look at the spike protein and see mutations that should reduce the ability of some of the antibodies generated by the vaccine to bind to the virus. So we think it's also finding ways to get around the immunity that we're generating in the population through vaccination.

But the virus also has lots of other mutations in other genes, and we don't know what those mutations might be doing. So we have some clue as to the changes that are happening, but labs like mine and many others across the country are spending a lot of time trying to figure out what else has changed in this virus to make it more transmissible in the population.

A change to the spike protein, which is what vaccines target, is somewhat frightening.

Absolutely. But you know, when we look at the changes that are in the spike, some of them are changes that we've seen with other variants at other times. That gives us the sense that there are a few mutations that give the virus an advantage—they make the virus better at transmitting or they help evade some immune responses that would normally prevent infection. And therefore those mutations start to appear in the populations that we're sequencing. And again, some of those mutations we've seen in other variants at other times, so it's telling us that the virus is "learning" to optimize the pathway and it's finding the same types of mutations that mediate better entry and better replication.

But that also means that because the same "dangerous" mutations to the spike protein occurred in other, less deadly variants, the spike mutation alone isn't what causes a variant to spread. It takes a combination of factors.

Yes, absolutely. And that's where looking at the virus genome itself only

gives us part of the picture. Oftentimes, other factors include where those mutations occur in the world. Is it occurring at the right time? Is it occurring in a situation where the virus can become dominant? Are there other strains to compete with it at that time? All those other factors play into whether a variant emerges and becomes dominant. So it's really a complicated scene.

To see something like the D614G variant first, then the Alpha variant and now the delta variant, emerge and out-compete other virus lineages is something that really catches the attention of virologists as something to be concerned about, because it is such a difficult thing for a virus to catch up to and surpass other lineages that have had a head start.

How quickly do variants emerge?

Well, first, viruses have a mutation rate that's much, much higher than humans or other animals, and they replicate at a rate that's really, really fast. So in other words, one virus-infected cell makes 100,000 copies of itself, and all those copies can go out and start replicating. So mutations occur randomly, but because the virus replicates at such a fast rate, you also accumulate mutations really fast.

But again, it's important to note that while mutations occur randomly, most of those mutations either do nothing to change how a virus behaves or they're detrimental.

Over the first year of the pandemic, we saw a lot of these mutations popping up that were allowing us to track the virus. We could say that a certain mutation occurred in England in this month and that virus strain started to spread. And we could trace back where viruses came from based on these unique mutations, but none of them really changed the way the virus itself replicated. It's only now that we're getting into some of these variants that are changing the way the virus behaves in the

population. And again, that's just a really small set of all the mutations that accumulate in these viruses.

Is it possible to prevent a virus from mutating?

Well, you can't prevent the virus from mutating, but what you can do is limit the virus's spread, and in that way you reduce the chances that a mutation can emerge that is going to help the virus infect humans better.

Say, for example, it's a one in a million chance that a mutation will be advantageous to the virus. If you let the virus replicate itself 900,000 times, odds are that the advantageous mutation will occur. But if you limit the overall replication of the virus to 1,000 times, then it's much less likely that the random advantageous mutation is going to occur. And that's where public health interventions really help us a lot during this pandemic—by reducing the total amount of virus replication and therefore reducing the chances that the virus can improve or adapt.

So, if we can reach a critical mass of vaccination, we can presumably drastically reduce the chance that additional advantageous mutations will take hold in our communities.

Absolutely. And I think we're seeing that now across the U.S., in places where there are good vaccination rates, you're seeing that the virus isn't spreading as easily. It's only spreading in unvaccinated people. So the strength of vaccination in terms of not only protecting people, but now limiting the emergence of other variants by reducing the overall replication of the virus in the population is clearly seen.

As new strains get identified—there's now a gamma variant, as well—what are we learning about the original SARS-CoV-2 virus?

Essentially it's telling us that that original strain—which surprised us with how well it was able to spread in the human population—still has room for improvement. The basic Darwinian principles of natural selection are in play now. The virus is changing to be able to spread better in the population, and when it gets better at spreading, it becomes the dominant virus—and we're seeing that occur over and over again. So clearly this virus came in with a good ability to replicate in humans, but it's finding ways to get better and become more of a human pathogen as opposed to what we used to call a zoonotic pathogen. This probably means it's going to be a human pathogen for some time to come.

Do you expect your lab to continue studying SARS-CoV-2 for a long time?

Absolutely. My lab has spent a lot of time studying influenza, and many of the same types of experiments that we do with SARS-CoV-2 give us very different results than the same experiment done with influenza. So while those two viruses spread in the same way and are causing disease in the respiratory tract, they do things in very different ways. And so it's going to be very important for us to understand how two respiratory viruses can cause such different disease at the molecular level.

While there's already been thousands of papers published on SARS-CoV-2, I think we've only scratched the surface in terms of understanding how this virus is causing damage in people—we don't really understand that in any detail. Comparing it to other respiratory viruses is going to be something that's really, really important for us to do because, again, that's going to tell us different signatures that we may need to look for in animal viruses that may tell us whether or not an animal virus is potentially a human pathogen.

But I would emphasize the important thing, which is the vaccines are still

working, and the vaccines are working against the delta variant—particularly the mRNA vaccines. If you've gotten the full course of mRNA vaccine, you've got pretty good protection against these variants. And that's just one more piece of data to encourage people to go and get vaccinated. These vaccines for COVID-19 overall perform much better than I think any of us scientists would have expected, and we really have a tool here that can make a big difference right now—nationally, but soon globally—in how this virus is spreading.

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