

Exchanges at Goldman Sachs

Is 2022 the endemic year?

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Translational Science Institute

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Allison Nathan: This is Exchanges at Goldman Sachs and I'm Allison Nathan, senior strategist in Goldman Sachs Research and creator and editor of the firm's *Top of Mind* report. In this episode, we're again focusing on the topic that's unfortunately been on everyone's mind for the past two years, SARS-CoV-2. The lightning spread of the Omicron variant has led to a record surge in cases globally. But its more transmissible but intrinsically milder nature has also raised the question of whether it's ushering in a more manageable endemic phase of the virus in 2022.

And the market, for its part, already seems to be moving on from worrying about the virus to worrying that it's now

time to pay the piper for the passive pandemic-era stimulus and the inflation surge it's induced. But is an endemic phase of the virus actually upon us? Given the important economic and market consequences if that is and isn't the case, the answer to that question is top of mind.

We first speak to Jeffrey Shaman, director of the Climate and Health Program at Columbia University's Mailman School of Public Health, for some context on what makes the Omicron variant more transmissible but less severe.

Jeffrey Shaman: The heightened transmissibility is hard to pin down why it is. However, early studies have indicated that the Omicron variant replicates in human lung tissue even faster than Delta does. Now, if it replicates faster, that means people get to a high viral titer in their body that is contagious earlier. If you do that, you shorten the latency period, which is the time from infection acquisition to the point at which you're contagious. You get infected with a virus, it has to replicate in your body. It has to make copies of itself.

And once it's made enough copies of himself and also where it is and what other things are going on, but a big

factor is how much of it is in your body is going to determine how much you're shedding, all right? And all things being equal, if you run a higher viral titer, you're going to probably shed more in your respiratory droplets and aerosols that you expel. And so my suspicion is that it has shortened the latency period.

Now, we saw very fast doubling times for this, and there's a lot of speculation. And our own estimates seem to indicate that, yes, there's a tendency towards inferring a shorter latent period. And that's consistent, to my mind, with those viral replication dynamics.

So if it's able to do that at a higher rate than Delta and Delta ran higher viral titers than Alpha and the ancestral variant, then it's able to outpace it and it can be more transmissible. And if it's more transmissible, then it's infecting people before Delta does and it starts to displace it in the population, which is what we saw. Because over the course of December, we went from Delta dominated to completely Omicron dominated.

The other thing of course is, because it has a larger pool of people to infect because there's this big chunk of people

who are protected against Delta but not against Omicron, Omicron has a lot more options to spread from person to person and can really spread faster and displace Delta entirely in the whole population.

So that may be the underlying basis for this heightened transmissibility. For the severity, this variant appears to take root more in the upper respiratory tract. You may hear that people are getting runny noses more with this than they did with the prior variants that we dealt with. And it seems to be setting up infection there and not doing as much damage to the lower respiratory tract where it can really mess with oxygen exchange and cause severe consequences, particularly the types of immune responses cytokine storms that are putting people at great jeopardy and killing people, frankly.

Allison Nathan: So should Omicron's intrinsically milder nature give us comfort that future variants will likely be less severe? Shaman says no.

Jeffrey Shaman: Is Omicron the harbinger of things to come? Is the virus going to become more transmissible and more mild as it goes along? This is going around a lot,

and there is a basis for these arguments in evolutionary theory. The evolutionary theory is that, as a pathogen sits in a host that it's just come to, it's going to evolve to be more transmissible and less virulent. Now, the first argument for the more transmissible centers on the idea of the mechanism for how Omicron outpaced Delta. That a variant that is more transmissible is going to run ahead of the other, it's going to infect people before the other variant does. And provided they provide cross-protection against each other, it's going to prevent that other variant from infecting the people it already has. And it's going to displace them and take over, and then its progeny are going to dominate. So there's a pressure to be more transmissible.

Now, this just doesn't happen willy-nilly. Influenza is not particularly transmissible, and it hasn't evolved to become more because of some kind of limitation in the virus and how it interacts with the host. It's kind of maybe met or reached its evolutionary optimum at this point and hasn't found a way to make itself more transmissible, so that's that.

This virus is new. It's only been in humans for a couple

years now, and it's still exploring the space of its capabilities, if you will. And its finding an ability to be more transmissible. We saw that with Alpha. We saw that with Beta and Gamma. We certainly saw it with Delta, and now we're seeing it even more so with Omicron. They're even more transmissible.

Now, the flip side is this idea of being less virulent. And that is centered in the idea that, if a virus or pathogen kills its host before its host is able to transmit it onward to other hosts, that's not in the variant's favor, right?

Because it no longer has the chance to spread, and it's essentially killing its own opportunity for transmission.

Ancillary to that, if it kills too many of its hosts, eventually it will run out of people to infect as well. So you don't want to kill off the host population to the point where the virus can't sustain itself and transmit.

The problem here is neither of those apply to coronavirus. It's just not there. This virus is shed before people are even symptomatic. And the lion's share of transmission is taking place among people who are not aware that they're sick or not in hospital and certainly not at the store. So the vast majority of transmission is taking place before

anybody dies, so there's no selective pressure there. And it's not killing enough of the human population. It's a little crude to put it that way, but, you know, maybe 20 million people have died from this, which is an enormous number but there are 7.7 billion of us. It has not depleted the pool of people it can go through.

I don't see any mechanism by which this is going to evolve to be milder. So the question then is, well, what's going to happen in the long run? And the narrative, well, this is a harbinger of things to come, the descendants of Omicron are going to rule I think is completely wishful thinking.

The reality is, if you look at the phylogenetic tree, it spreads out. There's this ancestral variant that emerged back in late 2019. It spreads out. There's a whole wing of Delta variants over here. And Omicron's way over here on the other side. Where is the next variant going to emerge on that phylogenetic tree? The answer is I don't know. The thing that's going to select for a successful variant is the one that can evade immunity. So why would it be like Omicron? Why wouldn't it be at a completely other location so that it can really evade immunity, get around, and cause a lot of infections and reproduce itself?

Allison Nathan: We also spoke to Dr. Eric Topol, founder and director of the Scripps Transitional Science Institute, who takes issue with the characterization of Omicron as mild altogether and generally agrees that we don't know what the next variant will bring.

Eric Topol: So when you say it's more mild, it's basically a wash because you have a million infections. So you have, like, five times as many as you've ever had before, right? And let's say it's 70% less severe. Well, if it's 30% as severe in a million people, you still have more people that are winding up with severe disease. So the idea that it's so mild is a misperception in many respects because we have so many more people getting infected. I have to respect this virus more than ever in terms of where it can go. I don't know if it can get worse. I hope that Omicron can be kind of our last stop along the way towards an endemic state, but that's very unlikely.

There was some evidence in the 1918-19 influenza pandemic that the last wave was a less severe one, but there were three waves there. We're already, like, in our fifth wave. You know, this is a different animal, a different

virus. We've seen striking evolutionary changes. The unpredictability of how we got from Delta to Omicron is a bit scary because we have a lot of brilliant evolutionary virologists. I mean, that's what they do. They figure out how a virus is going to evolve. None of them pegged Omicron as the next variant. They all pretty much thought it would be some lineage of Delta.

So Omicron was a major curve ball with all these new mutations littered throughout the virus, not just in the spike protein but even elsewhere. So that gives us a new sense of unpredictability. And if we keep going without containing the virus, without global vaccine equity, without boosters where it's needed, we will have another variant that could potentially be a true immune escape, not partial but true, absolute, which will blow through our vaccination coverage and our boosters. So I think we could go to a worse state. I like to be optimistic that we won't see something worse than Omicron and that this is the way we get all this population increased immunity that helps build the immunity wall better. But there's a lurking potential for a new Greek letter that truly does evade our vaccines and our immunity. And that, it would be the worst-case scenario right now.

Allison Nathan: But despite the risk of a variant that's more severe, is there at least some hope that the combination of prior infection, vaccines, and boosters will provide at least partial protection against new virus strains? On this point, while Omicron has evaded existing immunity more than prior variants, Topol believes we're actually lucky that our immune response has held up as well as it has, which may not be the case in the future.

Eric Topol: We are extraordinarily lucky here. And the immediate point is that Omicron, when it presented such a different version of the virus to us that was remarkably mutated compared to any prior version, it could have been seen by our immune system as much more foreign, alien than it was. Whereby, our B cells and T cells, our memory immune system, not so much our antibodies, can recognize it. And when our vaccines that we already had, the two shots, they were about 50% effective against hospitalization, which is better than nothing. But they were 90% effective with a third shot or even greater than 90%.

So the point there is that we could have easily lost our vaccine protection or protection from prior infections if

Omicron had even more profound immune escape. So that is on top of the fact that we got vaccines that were remarkable from the get-go at a speed that was in 10 months, which normally takes 10 years, and they were 95% effective and that you could give an extra shot of it that was directed against the original strain, ancestral strain, and it would work two years later against a strain that had profound antigenic shifts.

So what we're talking about here is I think most people forget about how lucky you are because we're seeing millions of infections and still people are dying and in the hospital. But, look, we could have fared far worse.

Allison Nathan: Shaman, for his part, is somewhat optimistic that our immunity wall will provide some protection against future variants. Here he is again.

Jeffrey Shaman: You have the population of the world going from being completely naive, having never been infected with SARS-CoV-2, to everybody having been infected and/or vaccinated and maybe multiple times. And those prior exposures confer some protection. They very well may be a good chunk of why Omicron is milder. The

other factor may be the fact that it's not getting into the lower respiratory tract as the same way and that this variant is intrinsically milder.

But there's a component of it that's likely also due to preexisting immunity that we've developed over the last two years from all the exposure and vaccination. It appears that, even though people are able to get infection from something like Omicron, that components of the adapted immune system, even though they're not providing what's called sterilizing immunity, preventing infection altogether, and they're not preventing symptomatic illness in some instances for some people -- there are asymptomatic infections around certainly -- it's still more likely to provide protection against the severe critical and fatal outcomes -- hospitalization, ICU ventilator use, and death.

And the reason may have to do with how the adapted immune system responds. The fact that the antibody titers are not high. The fact that the variant gets in and infects somebody, and then the adapted immune system ramps up and the reactive T cells get engaged the way they should. And your memory B cells produce antibodies. And even if they're not binding effectively, you can produce a lot of

them. And those things together are able to clear the variant before it mounts into something that was what we saw in the first year and a half of this pandemic.

So if people are boosted every year or every six months if need be and if that vaccination and our prior infection history protect us against the variants the way they have with Omicron, then what we're going to see is something like Omicron, where it's not causing as much death but it's running through the population very, very fast. It's crashing hospitals. It's really straining those systems because, even though it doesn't have the case hospitalization rate that we saw early in the pandemic, because we're getting so many cases all at once, it's problematic.

Allison Nathan: But despite some uncertainty around whether immunity from prior infection and vaccination will provide lasting protection against future variants, both Topol and Shaman see Pfizer's new oral antiviral drug, Paxlovid, as a game changer in terms of preventing severe disease and providing a bridge to a more manageable phase of the pandemic. Here's my discussion with Topol about this.

Let's talk a little bit more about that, the Pfizer antiviral that's had a lot of success in the trials. You're very, very optimistic about it. Why is that a game changer? How does it work? And given that, how optimistic are you that it could be effective over other variants?

Eric Topol: Yeah, I called it a just-in-time breakthrough. And the reason I label that is that here comes Omicron. It has profound immune evasive features. That's its main distinguishing property. And we are relying on our immune systems, whether it's vaccines or whether it's monoclonal antibodies, which turn out not to work. So relying on the immune system versus having a pill that is variant-proof works across all variants because it doesn't need an immune system. All it does is it takes down the main protease, M-pro, of this virus and it stops replication so that, if you take the pill, within the first few doses, you get tenfold reduction in your viral load. And that's one of the points that's missed about that, is that it really stops viral replication.

It's the first drug that's directed to this virus specifically. Any other medication has been repurposed by

dexamethazone and other things. This was the first one that it was a SARS-CoV-2-specific drug. And it was done in record time. Basically a small molecule that was within two years went through clinical trials with 90% essentially efficacy of hospitalization and death prevention. That normally takes over a decade at least. So the fact that it's held up and the safety is as good as placebo, maybe slightly better than placebo, I mean, how do you get to that point? So this looks really good.

Now, we only have two small trials that look really promising. We'll know more when it gets out in the real world, of course. But to have an immune independent treatment that will not be affected by variants, that has very potent transmission block quickly and this efficacy and safety that's unprecedented, this is exciting, really, to me. Very exciting.

Allison Nathan: But how can we be sure that it will stop viral replication in other variants?

Eric Topol: Right. So the reason why, the business part of the virus is the receptor binding domain and the spike protein, which you've heard lots about. That's where it

attaches to cells, gets into cells, and then hijacks the cell and makes a gazillion copies, right?

Now, it turns out that there's another part of the virus, the main protease, M-pro, which is not in that part where all these mutations have occurred. In the two years that this virus has evolved, there's only one mutation in this portion of the virus, an M-pro. It's not a part of the virus that does mutate. And Omicron, I mean, it just doesn't see Omicron any different than Alpha, Beta, Gamma, Delta. So unless something happens to the virus that's unusual over the course of time and we develop some M-pro mutations where we develop relative resistance, this appears to be as good as it gets because we don't rely on inducing an immune response. It just is directly inactivating the virus at its choke point. You just can't design a better way to get at the virus than this.

Allison Nathan: So based on what we know about future variants, our immunity wall, and the efficacy of existing vaccines and treatments, the key question is: Can we expect to be in a more manageable endemic phase of the pandemic in 2022? Both Topol and Shaman cautioned that it may be too soon to think that's the case given that

we don't know what the next variant will bring, though they believe that a more endemic state for at least parts of the year is possible. Here's Shaman.

Jeffrey Shaman: We would like to stop obsessing about it, and we would like to stop having the disruption. So endemicity is the persistence of a pathogen within a community or population. The fact that it is there with some rate or some recurrence, if it's seasonal, is the endemic pattern to which it falls. In order to have a pattern, you have to look at it for a long enough time, which is why it's analogous to climate. You don't know what the average temperature of a location is by looking at a couple years. You need to look at 20 or 30 years of record in order to get a good sense of what actually typically goes on. I'm not saying we need this long for this virus, mind you. But it is something to consider.

The endemicity of this virus will be how frequently we are having outbreaks and the severity of those outbreaks, the burden that it imposes on us. We would love for it to evolve into something like OC43, that endemic coronavirus, that is wintertime seasonal, there are lots of variants, people can get a bit out of season, they can get multiple

infections, but it's very mild. That's not going to magically happen for this virus.

What is potentially going to happen is that growing immunity and exposure to variants over the years may confer enough protection on us that it becomes milder for individuals. That partial protection we have results in protection against the more severe consequences of it, so you get a sore throat and some body aches, you may miss a day or two of work like you would with the flu, but it's not going to put you in the hospital in the same way.

You can imagine that, if this virus stays with us -- which there's no reason it won't and I can't see any reason for it to be eradicated; we have a very tough time doing that -- that people born today will get exposed to it when they're very young. They'll get infected. They'll build up immunity. Children are at very low likelihood of hospitalization or death from it. Hopefully it doesn't have severe long-term consequences. And that early exposure to variant, or most likely variants, will provide protection that later in life prevents them when they're adults and they're more likely to have severe consequences from having those severe consequences that we saw during the pandemic

phase.

So in other words, the way it becomes milder is because of the exposure we've had and the exposure is had because of infection nationally and vaccination. Those are the ways that we can confer protection on populations. But the narrative that we have is that the virus itself is going to become milder isn't. The other thing is that we are really conditioned by flu and by the fact that in the United States we get wintertime colds and flus to think of it as a once-per-year thing. And it may not be that way. It may not be that way in the short term, as it's figuring out as much of the new variants as it can spring on us, as it's basically getting sent to the space in which it lives. It might not even be that in the long term.

Because it's so much more transmissible than the flu, it's possible that we could be looking at multiple outbreaks of this. There are places in the world, because of their climate, that have multiple outbreaks of flu per year. And it may be that that's what we wind up here. Not saying it will be, but that's something that's really to be determined, I think, by seeing what happens.

So we would love for this to devolve to the point where people can go about their lives and let medical and public health establishment think about the virus and help manage it and not have it be the leading story on the news five to seven days of the week, right? And I do think it's quite possible we'll get to something like that this year, at least for parts of the year. But we're still going to have to obviously be cautious because we don't know if a new variant is going to come around and be more problematic.

Allison Nathan: And here's Topol.

Eric Topol: How are we going to get to this endemic stage where it's kind of low level and you're not too worried about it at any given day except if it just happens to be an outbreak that erupts in your area? There were two routes to go. The first route was that we got Americans really behind the vaccine and had 90% vaccinated of the population, which we could do but we haven't and we're at 62%. We're never going to get there because of the anti-science, anti-vax. So we're not going that route.

The other route we can go is a pan coronavirus vaccine that people get and Paxlovid or equivalent that we all have

available. That's certainly not going to be in every medicine cabinet this year. I mean, it'll help but it's not going to be enough.

So are we going to get to an endemic state? I hope so, but we haven't used the tools we have, either because we ruined our chance with the original plan or we haven't developed what we could right now to give us ultimate confidence. I would have ultimate confidence right now if I had had a pan coronavirus vaccine and I had Paxlovid in my medicine cabinet. I wouldn't worry at all. But we don't have those things. So I tend to be thinking that we'll get to an endemic state this year, but it's still tentative because there is this one big unknown which is what do we see after Omicron? And that may not even be in 2022. It could be in 2023, 2024. We just don't know about that.

We should have the highest regard for what this virus can do because it's already thrown us one of the most extraordinary curve balls in the history of virology.

Allison Nathan: With the state of the virus likely to remain important for the health of the global economy and markets as well of course for world's population, we'll

continue to closely watch its evolution from here. I'll leave it there for now.

If you enjoyed the show, we hope you subscribe on Apple Podcasts and leave a rating or comment. I'm Allison Nathan. Thanks for listening to Exchanges at Goldman Sachs, and I'll see you next time.

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