Mutations & variants

[00:00:15] **Deborah Blum** I'm excited also about this panel in which we look at the evolution of viruses and the emergence of variants and where we think this apparently endless pandemic is going, we hope it's not endless. We have an absolutely wonderful panel here. We have Angela Rasmussen from Canada, Purvi Parikh from the United States and Kai Kupferschmidt from Germany joining us today. And thank you so much for being here you all. I've been really looking forward to this conversation, and I want to start with Angie just talking a little bit about what we understand about the way this pandemic has evolved and by evolved, I mean the virus itself. So, we started with one version of SARS-CoV-2. We've gone through a number of other iterations. We're in the Omicron at the moment, but we are seeing variations on the ground itself. Could you talk a little bit about some of the factors that have sort of brought us to this point? And the way I think I am wondering if human behavior has influenced this viral evolution, Angie?

[00:01:40] **Angela Rasmussen** So that last question is a really, really difficult one to answer. Certainly, humans have obviously influenced this virus's evolution. Behavior is a little different because then you get into how is behavior contributing to transmission, which is really the scientific basis for the virus and the variants that we have circulating right now. I think one thing that that I've observed throughout the pandemic and it's been very interesting because I'm an RNA virologist. To me, it's not surprising that if you take an RNA virus like SARS-CoV-2 or any other RNA virus and you let it basically run free in the population, you are going to get new variants evolving. But the way this is often covered is really credulous and it's oh my god, I can't believe we've got another new variant. I think that human behavior certainly comes into effect in the fact that we're all extremely tired of this pandemic, virologists included. And it's like, oh, no, another variant. But it's not surprising. I guess I should say the things that are surprising about the variants to me anyways are not the things that are often shown in the press as surprising. So, like, for example, it's not surprising that again, if you have an RNA virus, which is going to mutate every time it replicates and you have that spreading between millions, billions of people, you are going to get a number of new variants, the virus will continue to evolve and adapt for its host. In this case, that's the human population. But I think what is surprising to me is that every time we have a new variant emerge, people are still acting as though this is a surprising outcome, which again, it's not. The things that are surprising, specifically with Omicron to me, are the fact that Omicron may have a bit of a different origin than some of the other variants of concern that have emerged. So Alpha, Beta, Gamma and Delta all emerged during unchecked transmission in largely unvaccinated populations, and that's not really the case with Omicron. So, Omicron did emerge or at least was first detected in South Africa and in a part of the world where the vaccination rate is overall low. But population immunity may still be high because they have had quite a bit of transmission in earlier waves caused by other variants. Evolutionarily, when you look at the genome of Omicron, it doesn't look like it evolved from viruses that were circulating recently in the human population. So, there's really three hypotheses for where Omicron came from. One, that it was the results of long-term cryptic transmission in a population that's not being surveilled, meaning a population of people where it was spreading and it was not being detected by genomic surveillance and sequencing. Two, that it was the result of long-term infection or persistent infection of an immunocompromised person. And three, that it was the result of what's called a zooanthropronotic transmission, or spill back, meaning at some point spilled back into an animal population and then spilled over again into the human population. So right now, we don't we don't really know where Omicron came from, but it does appear to have somewhat of a different origin than the other variants of concern. Again, this isn't particularly surprising just when you think about the biology of

RNA viruses. This virus, in particular, is a generalist. It can infect a number of different species. We would expect to see the virus continue to evolve and adapt to whatever host it's in. But this has emerged in a different way than the previous variants of concern and the fact that we're still kind of talking about it as though, oh my god, it's such a surprise this is a new variant. Well, we've had four other variants of concern, and there are many more variants of interest that have been identified. So, I don't think it should be that surprising that we have new variants emerging. When it comes down to human behavior, I think the thing that we need to be focusing on rather than, oh my god, new variant, is that our behavior is directly contributing to these variants emerging. And that means that we're not taking the proper precautions to reduce transmission, we're not making vaccines accessible to everybody in the world and we're not doing the things we need to be doing to reduce transmission because that is what is going to reduce the emergence of new variants.

[00:06:11] **Blum** Yeah, those are excellent points, and I'm going to circle back to a number of them, I want to jump over to you, Purvi and ask this. There's been a kind of mythology surrounding Omicron suggesting that at least early on, that it was milder than some of the other variants. It's certainly if you look at hospitalization and death rates in the United States, that's kind of hard to believe. Could you talk a little bit about what we know about whether this really is a milder variant or is it more the current state of vaccination and previous exposures that makes it look that way and just the whole interaction so that we can become more accurate idea of what you think is going on?

[00:06:59] **Purvi Parikh** No, those are all great questions. And you know, even the word mild sometimes makes me cringe because I think it's the wrong word because it conveys the wrong message to the general public that this is not something to be taken seriously and kind of echoing what Dr. Rasmussen said, this is contributing to human behavior, right? Not taking those precautions in combination with the pandemic fatigue. But that being said, I'm a clinical immunologist, so I'm seeing this in patients both in the hospital, out of the hospital. Even most of my research is clinical research, and what we're seeing is that, yes, that in some cases we are seeing, quote unquote "milder forms," meaning those who are vaccinated or even boosted, is not progressing to the point where they're thankfully needing hospitalizations or ICU admissions. But that's not an absolute. Every day we're seeing people get admitted who were vaccinated, were boosted and even those quotes unquote "mild people" in the outpatient realm that are recovering at home. It's not a cold, and I'm speaking to people across all ages, with all different medical problems. People are knocked down by this and not just for the time that they're infectious, but we're even seeing for weeks afterwards. And a particular interest of mine is long COVID-19 or, you know, the post-acute sequelae of COVID-19. And we know very well from previous variants that asymptomatic disease, mild disease can still cause very debilitating long COVID-19 syndromes. So that impact with Omicron, I'm also kind of nervous to see. So, when it is described as mild, at least from a clinical standpoint, that concerns me. And it's not meant to cause panic or worry, but we are seeing the crushing impacts on the hospital systems and we're seeing that even if, let's say, the COVID-19 infection is not the primary reason for a hospitalization or an ICU visit, it's actually exacerbating their underlying condition. So, we're seeing a lot of people coming in with their heart failure uncontrolled or their diabetes uncontrolled, and it wouldn't have been uncontrolled had they not gotten that infection right because we know all infections can cause chronic illnesses to kind of go haywire. So that's the one side. But then the other side of it is that in the unvaccinated individuals, it's not mild at all. We're still seeing those individuals get intubated. We're still seeing those people pass away even with the Omicron variant and have a lot of long-standing effects. In fact, the first death in the U.S was somebody who was unvaccinated

but had previous exposure to COVID-19, so. So again, you know that nomenclature mild doesn't sit well with me, and I know that there's been thoughts that this is less neuroinvasive or this is more an upper airway, which is true. It does replicate more in the nasal passages, in the throat brinjal passages. But is it milder? Because now, so many individuals are vaccinated and then about a third of those individuals are boosted now. We don't know, is it a combination of the actual variant being quote unquote "less severe," or a combination of the vaccine plus the variant? And I think it's very hard to tease that out. You know, it's one of those chicken versus egg conversations.

[00:10:29] **Blum** Yeah, that gives it exactly the kind of nuance I was looking for and Kai jumping over to you, do you think that some of this perception that Omicron was less destructive to just pick a random word there? It's certainly there were a lot of journalists who reported it that way early on, and I'm wondering if we have some responsibility for, you know, the sense that this was not that dangerous and if that sense encourages more risky behaviors or is it just that our understanding of what the variant was changed, so we were sort of figuring it out like everyone else as it went?

[00:11:15] **Kai Kupferschmidt** Yeah, it's a really good question. I think what fascinates me about the variant beat, almost like I feel like I've been reporting on variants now for over a year. And what fascinates me about it is that there is so much uncertainty early on and there is, I think Federico Kukso was giving a kind of impassioned plea earlier in the other panel about, you know, following the evidence and you can't really do that with the variants because in the beginning, there just isn't any evidence. And so, you end up having to write a lot about what we do not know, why we don't know it, how are we going to find out about it? And you also have to choose very carefully who you talk to because you are when you're going to get opinions in a sense. But it does matter what the track record is of these people and what expertise they have. And so, I found it really difficult, especially with Omicron, because this narrative came very early on from South Africa, where people were saying, you know, doctors were saying, ok, we see a lot of mild cases, and it was very clear at that point that you wouldn't be able to just take the South African experience. You know, they had 70% zero positivity in Gauteng province. So that means 70% of people that already had antibodies against the virus and even though they had very low vaccination rate of about 20% at the time, and it was clear that you can't just take that and apply that to any other place in the world and then assume that the same thing happens. So, you have to give these caveats but I also think that over time, you do have to then shift your view and I think this is something that with Omicron more than the other things is becoming very difficult. I think with Alpha, with Delta, there was this sense of this could be bad, this could be more transmissible, it could even be more severe, but we have to wait for the data, this is what we know so far. And then it turned out they were more transmissible; they were more severe and it was a problem. Now with Omicron, the situation is different, and I think there is a sense now that a lot of people have just a frame how they think about these variants. And we have to shift it a little bit because this is the first variant that's a real immune escape variant. So, it is a little bit different from the variants we've seen before. I do worry a little bit also that we give these variants too much agency, almost in a sense. So, while it is important to look at the- well all the characteristics of a new variant and what that might mean, the more important thing at the moment worldwide is the question of what's the immune population, what's the immunity of the population that this virus is spreading in? And so, I'm having a hard time sometimes now, you know, when I'm talking to friends, when I'm talking to people on Twitter explaining that, you know, whether it's Omicron or another variant, we are in a different situation than we were, say, in December 2020 or in March 2021. The risk has gone down, mostly because of vaccination, and I think that is something that you have to communicate

as well. I think for a science journalist, the risk is sometimes that we are the ones who are very- who want to be really careful about these things and so we explain all the caveats early on. But I do think you are also at the moment have to accept that there is a difference in the risk scenario and I find it really interesting if you take the U.S. where you have a lot of people really not changing the risk perception as people mostly, on the political right who never thought this was dangerous, even though that was completely misguided and they haven't really changed their view on that and then on the other hand, you have the opposite, which is that some people who are triple vaccinated are as risk averse now as they were a year ago, and I think that's also not right. So, the virus is going to keep producing these variants, but we are going to have to really take more than just the variant into account when we when we decide how to deal with it. And just one last thing when I talk about agency with the virus, I think it's fascinating to me, if this seeps into all the reporting we do, we kind of write that Delta replaced Alpha and Omicron replaced Delta. And these things, it's not that this virus just comes and shoves away the other one, in most places, Alpha was going down before Delta arrived because we instituted measures that pushed the R of Alpha below one. But then Delta came along. It was more transmissible, and so our measures weren't enough and so Delta was increasing while Alpha was decreasing. We did that. It's not that the virus just came and pushed to Alpha. We actually managed to control Alpha and then Delta came. Very similar situation in a lot of places, take Germany. Delta cases were going down because of the measures, now Omicron is coming and the measures aren't enough, partly because it spreads in vaccinated people as well. So, there is a question of how we tell these stories and how much agency we give ourselves versus the virus, and I think if we give the virus too much agency, it feeds into this kind of sense of almost fate or inevitability, which I find so, so destructive at the moment. I'm reading a lot of old science fiction from like the 30's, 40's, where you have this kind of more techno optimistic sense. And I'm just realizing that I'm really- I mean, there's a lot wrong with that as well, but I'm missing the sense that we have a huge problem but here is the agency we have, here's is what we need to do instead of sometimes framing these stories as if we're just victims of fate.

[00:16:47] **Blum** Yes, I think that's an excellent point. I mean, I will say from a U.S. perspective that a lot of science journalists here recognize that we have all these tools and people won't use them, so you also get a sense of banging your head against some kind of wall in which you're trying to get information out. And it really goes back to one of the I think the questions are journalists, we're not advocates. So, what we're supposed to do is give this honest information and then hope that people are going to respond in a reasonable way and jumping backwards for a minute because your talk about sort of the way we see variances was really interesting to me. One of the stories that I remember from early on Angie, was that this coronavirus was not going to be all those mutants. Thank goodness there wasn't a flu virus that we could come up with protective measures and they would have some stability. And maybe it's not as shifty as a flu virus to use a kind of popular word. But it does seem like, did we underestimate the ability of this virus to change early on?

[00:18:06] **Rasmussen** No, I don't think we actually did. I think, though, that those assumptions were based on the fact that we would be able to control this the way that we controlled the SARS classic epidemic. And that was fairly easily controlled. I mean, it wasn't, but infected 8000 people, partly because it was less transmissible than SARS-CoV-2 but also partly because people were able to implement public health measures that really did control it's spread even after it spread to Canada, for example. People were generally being febrile so you could you could identify cases based on symptoms. There wasn't as much pre-symptomatic transmission, so it was a lot easier to control the SARS

classic epidemic. And I think we made a lot of assumptions early on, obviously wrongly, that that we would be able to do the same thing with this and that we would not have a situation where there is ongoing transmission and there are ongoing surges where a lot of people are getting infected all at once effectively. I think that the one thing we did know ahead of time is that this was going to have a mutation rate that was similar to other coronaviruses. And it's correct that coronaviruses, unlike or a mix of viruses like influenza, cannot reassert. So, their genome is one piece. It's not eight separate pieces the way that the influenza genome is. So, it can shuffle up and mix with other coronaviruses as easily. There's also not a lot of other human coronaviruses that would necessarily be compatible for SARS- CoV-2 to recombine with. So, we know that- also coronaviruses I should add, have something that most RNA viruses don't, and that's limited proofreading capability. So, they still have a higher mutation rate than a DNA virus or another organism that has DNA as its genetic material, but it's lower than most other RNA viruses, so they do have a lower mutation rate. And I think we made those assumptions that it wasn't going to be assort. There weren't going to be dramatic changes in antigen necessity in terms of the immune responses that it invokes or elicits, and that it also wasn't going to get the opportunity to replicate as much as it has because it has had so much opportunity to transmit through the population we are seeing, it's just really a numbers game. We're seeing the number of mutations that we would expect with widespread transmission among billions of people.

[00:20:38] **Blum** That makes sense. And then so when we see Omicron as a wave and I will tell you that this is the first of the waves in which many people I know got COVID-19. I mean, I felt like my fellow science journalists and I were all hiding in our houses for two years, essentially, and no one got sick and then suddenly, I know so many people who have, is this predictive of continued mutation and variation? And I'm just thinking of human hosts, I do want to come back to the animal hosts question, but I'd like to actually ask all three of you, is there anyone here who doesn't expect another variant of interest or variant of concern to arise?

[00:21:24] **Rasmussen** I mean, I can start we have three billion people in the world who have yet to receive a vaccine dose so absolutely, I expect another variant to emerge, whether it's going to have the same properties as Omicron, it's going to be more transmissible, potentially more pathogenic. Equally, as immune evasive, who knows. But certainly, those are all possibilities on the table. Certainly, Omicron has spread widely enough that now and we are already seeing this, that there are sub lineages of Omicron that appear to be out competing Omicron original recipe, at least in Denmark. So, I think that that we can certainly expect more variants, at least that are Omicron sub lineages, but I'd be very surprised with the current state of the global population in terms of immune status if we didn't see more variants emerge.

[00:22:13] **Blum** Purvi?

[00:22:15] **Parikh** Yeah, no, I agree completely, not only that, but I think at this point it would be really foolish of any of us to really try to make any predictions. Because what the one constant is change and unpredictability in this pandemic, and there's so many factors that go into that. Human behavior, the delay of the vaccine rollout so absolutely it's only a matter of time now. The main question would be how are our current vaccinations and efforts? Will they hold up against those future variants? And that story remains on hold. I'm still fairly optimistic. I know so much of this pandemic has been focused on antibodies, antibodies, antibodies, but myself, as well as many others have been since the beginning, screaming. But look at the T cells. And there was a great review in Nature recently that spoke about bats, specifically natural killer cells, that the glimmer of optimism is that these

cells still recognize Omicron very well, especially where the antibodies fail. And that's actually good news, in my opinion, because it's those T cell responses that we get from the vaccine and beyond that really help, I think blunt very severe disease, meaning hospitalizations and deaths. So, let's see, I mean, a lot is unknown, but I think we can all bet on there likely will be another variant of concern, especially given the vaccination issues and others. It's human behavior general.

[00:23:44] **Blum** And do you agree, Kai?

[00:23:46] **Kupferschmidt** Yeah, I certainly do. And maybe let me run through, four points really quickly. So, one, when we talk about variants of concern, we usually use the W.H.O nomenclature. Now, Omicron is interesting because actually, Omicron is a lineage that technically doesn't really exist. It's a parent lineage of several different lineages. So, in the beginning, Omicron, what we mostly saw was something that's BA1 in the pangolin lineage and- no, that's actually, I think that's an extreme lineage. Anyway, there's a lot of different nomenclature, which is an interesting problem when talking about these things. But so, there's BA1 and there's BA2, which assist the lineages, and we're now seeing BA2 maybe displaced BA1. Certainly, we see it in Denmark, we see it in the UK to some extent. Again, all the caveats apply. You know, you can talk about this for 50 minutes, but basically it suggests that it might have a transmissibility advantage. What exactly that comes from, we will see. And if that's the case, it could be, for instance, that the W.H.O. at some point decides that BA2 gets its own its own name. Part of the problem is that BA1 has a specific mutation that allows us to detect it fairly easily, it's the gene dropout which we already saw in Alpha. So, you can see it in certain PCRs. And that's not the case for BA2, which is why is sometimes called a stealth variant, but that's- I find that a bit annoying, to be honest. And so, it is possible that that's already the next variant, which would be really interesting because that's a pattern we haven't seen so far. I think the second point I want to make is just we are probably also going to see recombination. There is another system lineage called BA3, which seems to be a recombinant of BA1 and BA2. Again, there's a lot of caveats, but that's what we think is probably the case. Now, it's absolutely possible that we're going to see recombinant, for instance, between Delta and Omicron, what they would look like is anyone's guess. I think I think it's really simplistic to just assume that they're going to be as immune escape as Omicron, but as fit as Delta, it could be very different. So that's in a way really fascinating actually for me to kind of to think about and to find out what nature ends up coming up with. And the third point is that this is the first immune escape variant we've seen, and I don't think there's any reason to assume that this is all this virus can do. It has shown us one possible kind of constellation that allows it to escape the immunity that we know have in humanity. But there could be a lot of other constellations. And if you do an antigenic map and you look where these lie, it could be that the. virus goes off in a different direction. It could be that we finally get a kind of second-generation variant of concern that actually builds on the previous month. So far, every variant of concern has had kind of an independent origin, which, by the way, to me, when we talk about origin questions, that is the most interesting question, though, because I think it doesn't really matter that much for the trajectory of this pandemic where the virus originally came from. It does matter a lot where these variants are coming from because they are going to keep coming. And the better we understand how they evolve, the more we're likely to actually be able to do something about it. Last point, I just want to push back a little bit against something that Angie said. And I feel like especially when it comes to evolution, we always have all of these narratives that kind of sound convincing but I'm not sure that we actually have the evidence for it and one of these is this talk about we need to share vaccines equitably in order to avoid variants from coming. We need to share vaccines equitably, because that's the right thing to do. It's the ethical thing to do, and it's

going to reduce overall the deaths and the burden of disease in this world. Every life on this planet is equally valuable, and it makes no sense to be booster in 20-year-olds in one country, while people at risk in another country, you know, don't get a single shot. No question about that. But if I look around the world at the moment, it is the countries that have the highest vaccination rate that are allowing themselves to let the virus spread unchecked. So, Denmark clearly is a place that you would expect maybe a variant to evolve. That goes against this idea that if we distribute the vaccines equitably, that reduces the risk of variants. The other point is that as long as we don't know how these variants really evolve, is in an animal reservoir? Is it in people who have chronic infections? What kind of people? As long as we don't really know what I feel like, we're overstepping if we say we know how to avoid them evolving. So, this is just one of those examples where I think we tell these stories and we understand why we tell them because there's a lot of very, very egotistical people in this world. And sometimes you have to- and you use this argument to argue for equitable access to vaccines. And it's easier if you tell people, hey, it's in your own interest, because that way the variants aren't going to come, we're just prolonging the pandemic. I get that. Doesn't mean that it's true and I think in the long run in all of these debates, we lose a lot of credibility and also, it's a chance to argue for ethical behavior for the right reasons, I think, which aren't always self-interest. I know that Angie agrees to a large extent. I think I just wanted to push back on that because in the broader public and also, to be frank by the W.H.O, it's been used a lot as an argument, and I think we have to be very, very careful with that.

[00:29:07] **Blum** Do you want to respond to that, Angie?

[00:29:09] **Rasmussen** Yeah, actually, I really misspoke. And this is probably a good example in real time of how you need to choose your words very carefully when talking about this topic, because I completely agree with everything Kai just said. And as I started off at the beginning, you know, saying, we don't really know where Omicron came from. There's no guarantee that vaccinating the world is going to stop variants entirely. And in fact, I mean, we are on the road, zero COVID-19 is not realistic. We are not going to eliminate this virus. There are so many species besides humans. We will not be able to vaccinate all of the susceptible wild animals, even the domestic animals on the planet that can be infected with this virus, so variants will continue to emerge. The real question is, how much does that matter to us? And that's where the vaccine equity argument comes in, because vaccine equity. So, people who are vaccinated and especially people who are boosted, are less likely to transmit the virus even and less likely to be infected, even though they can do more with Omicron. So, by and this really argues for really, the central point of what Kai was saying that we argue these things in self-interest, but we should be arguing them in terms of the population because when people are at population immunity- and this was absolutely the case with the polio vaccine, for example, which is not sterilizing, it does not completely prevent infection. And yet it effectively eliminated polio because polio can infect a lot of other animal species within ten years in the U.S., but that required a very, very high level of vaccination. So, we get enough people vaccinated there will be fewer variants emerging, probably because people will be getting less sick, they won't be such a public health problem, and overall prevalence, at least in the human population, will be down compared to what it is now. But Kai's absolutely right that the countries that are doing the worst and Denmark yesterday decided to pretty much raise the white flag in all of their efforts to control transmission. Vaccines alone cannot do that, so we need to apply other methods as well. We also need to be surveilling and looking for this virus so that we can apply some of these countermeasures if there is an outbreak of a variant that is more likely to spread in vaccinated populations. So, I agree with everything that Kai said. I think this is a great example of really needing to choose your words

carefully when trying to make these arguments because variants are here to stay. The question for the long-term outlook for us is how long are they going to continue to be a huge public health problem for us?

[00:31:50] **Blum** That is such an interesting conversation there. Purvi, do you want to add to it and or do you have a perspective on this? And I also wanted to ask you something that I've seen come up, which is the suggestion that being infected with Omicron might not be that protective against some of the other variants that it's unique enough and in its genetic structure that you might if you got Omicron definitely be resistant. I'm guessing the other variant of the Omicron variants, but not necessarily the Delta. Could you talk about both the vaccination point that was raised here, but also just the basic immunology of what we know about this variant?

[00:32:35] **Parikh** Yeah, absolutely. And I completely agree. Vaccines don't guarantee zero variants. They are supposed to just set us up for success. They don't also even guarantee zero infections. Case in point with flu vaccine and other vaccines- pneumonia vaccine. We see cases every year. The whole point is we want to reduce deaths. We want to reduce hospitalizations and hopefully reduce transmissibility, too. Because if you're less virulent, if you have less virus replicating within you, then theoretically you should be less likely to pass it on. So, I absolutely agree with that. But still, all of the points mentioned vaccine equity is important because everyone deserves to have that protection against the severe disease against that. But yeah, by all means, that's no guarantee. There are no guarantees. As for immunity, for Omicron and how that will play out with future variants, I mean a simple answer, like everything in this pandemic, we don't know. Whether resilient to variants thus far and if I was going to make a prediction, even though I said we shouldn't, and I would say that the T-cells will continue to be the most resilient and that is what varies the best. When you look at patients even early on in the pandemic who were undergoing cytokine storm in the ICU, a lot of these patients, they did show T-cell exhaustion. They showed severe lymphopenia. So, I believe those T-cell immune responses are so crucial now and for future variants, especially against that severe disease hospitalizations. And it may even give us a sense of understanding why certain individuals become so sick with this virus and why some don't. I really believe that there is something deeper there and I'm hoping more research is targeted there. But as for Omicron being protective against other variants, we don't know. But I do believe at least the T-cell immunity will be resilient, even though up to now we're seeing that antibody immunity is more invasive. That makes sense.

[00:35:27] **Blum** Yeah, that makes a lot of sense. And I have so many more questions, I'm like a question machine, but we have a ton of really wonderful questions from people who have joined this webinar. So, I'm going to shift over to that. I want to mention before we got started that earlier Dr. Maria Kerkhove from the W.H.O. was supposed to join us, but she was unable to do so due to a very recent time conflict.

[00:35:59] **Kupferschmidt** So Deborah, can I add one thing?

[00:36:02] **Blum** Yes Kai.

[00:36:03] **Kupferschmidt** Because I think I mean, as to your question about cross immunity, I think it is really fascinating because one of the things that maybe it hasn't sunk in yet so much is that there is, of course, the possibility that we are going to get several variants circulating at the same time. I mean, Christian Drosten, for instance, has for a long time argued that we are on the path now to getting a different serogroup. So basically,

this is what happens if you have one virus that doesn't produce immunity, maybe against one with a very different spike. So that adds a whole interesting layer to the evolution that we might be seeing in the next months. Because if this several of these variants, at least two circulating at the same time, it might become important for doctors to know which one certain patient has because it could decide whether you're using a certain monoclonal antibody treatment, for instance. It would also just add to the burden of disease. So, there is this whole- I mean, when we say the evolution of Omicron or the evolution of SARS-CoV-2 isn't over yet. I mean, there's a whole 'nother, you know, level of things that can start to happen now and we really have to see what this new world where we have a lot of immunity in the population, what that does to the evolutionary trajectory of SARS-CoV-2, and I understand that it's scary sometimes, but it is scientifically incredibly fascinating.

[00:37:28] **Blum** Yeah, that is such an interesting point, and I wish we had all the- I mean, one of the things that's very clear is we're still figuring this out, right? But man, there's so many interesting questions that this particular pandemic has raised. I'm not saying that's a bright spot in the idea that isn't it great? We had a pandemic so we can find out all these fascinating things, but it does raise really fascinating questions. And I'm going to start with questions from our viewers and they are divided into a number of categories. Purvi, there's a couple of questions raised about both viral reinfection and the fact that in some families, one person may be COVID-19 positive, but another person doesn't get the virus at all, even though they were heavily exposed. So, these questions running enough kind of they sort of hold hands. One is, did I understand that you could be infected by Omicron more than once, but first get it and then get reinfected? And there have been many cases in a family where someone has had COVID-19 and other members of the family do not get infected. Do you understand what's going on there? And this is from Susan Ruiz Peña and Jose Jimenez from Guatemala.

[00:38:53] **Parikh** Right? Yeah. So, it is possible, albeit very, very rare, to have Omicron and get reinfected again. There have been cases that we've seen. What's been more common is that we've seen people that have had other variants or other strains then get Omicron because mutationally it is so different. But also, again, that's also not exceedingly common. Right. So that's also very, very rare. But what I'm saying is that it is possible, including the death that we saw in the U.S. That was a gentleman who was exposed, we believe, to Delta and then developed Omicron and ultimately passed away despite having that previous exposure. So, these are very interesting. As the virus continues to evolve, I think we may see more cases of it. And then also to Kai's point, I mean, I do believe that are their strains and Delta is still circulating and we knew as recently as around Christmas time, you know, initially, the CDC had said Omicron was the most variant strain. Then they backtracked and said, oh, actually, it's 60% Omicron, 40% Delta. So, a lot of those infections that even occurred in December, I believe, were likely Delta, especially some that still behaved as quote unquote "Delta," with those still neuroinvasive symptoms with the higher fevers with different lower respiratory symptoms as well. So again, yeah, is it reinfection with the same variant? We don't know. Is it reinfection with different variants? And now, you know, as Angie and Kai have noted, that there's even variants of the Omicron itself. So, all of this has to be teased now, I think its very interesting question is that will we now have testing that's variant specific because I think as a clinician, that would be huge, right? Because certain hospitals in my region stopped giving monoclonal antibodies at one point because they were like, ok, that's not going to work, it's only Omicron, which I don't think was the case. I think there was still Delta occurring and maybe people could have benefited from Regeneron monoclonal antibody treatments while we waited on those Sotrovimab antibodies to arrive in our state. So, all very interesting questions, and there's no easy answer.

[00:41:14] **Blum** So there are some questions about BA2 to here. And interestingly enough, I'm going to tie it to a question from Esther [00:41:27] Whitmer, [0.0s] which is do variants die? And I think that not necessarily, but variants, as I understand it, can be out-competed. So, one of the questions here is whether we expect BA2 to out-compete BA1 with Omicron? And do we think it's going to lead us to more severe illness?

[00:41:54] **Rasmussen** So I guess that's probably for me, the first answer is we'll see, we have seen that BA2 certainly seems to be doing better than BA1 in Denmark. And as I mentioned, also potentially in the UK, we'll really have to see how they perform in sort of a head-to-head variant off when BA2 has been imported to other countries. So, we'll see how that does. So, we don't really know, but I think that in terms of do variants die, that's a very interesting question. And it's one that for virologists, you could probably have like a week-long seminar on it because people still don't agree whether viruses are even alive in the first place. But variants certainly can become extinct. So, any virus has to have a host in order to reproduce in order to replicate. If it doesn't find a new host or if there's already another virus there that prevents infection and successful replication in a host, then eventually, yeah, that virus will become extinct. And we've certainly seen that early lineages of SARS-CoV-2 are no longer circulating, at least not in the human population. And Omicron itself is actually- this is one of the big mysteries about Omicron, and its origins is most closely related to viruses that were circulating in the human population in mid-2020 and late spring, early summer 2020. So, where that virus went in the meantime is, again, there's several different hypotheses for where it could have gone. But viruses in the human population variants can certainly become extinct out, competed or at least circulating at low enough levels that they're not going to be recognized by the genomic surveillance systems that are in place, which are very, very patchy and certainly aren't covering the entire breadth of the coronavirus variants that are circulating right now in the human population. We have no idea what's happening in the animal population, for the most part.

[00:43:59] **Blum** I want to just stick with that animal population question for a minute. And we know that's true with influenza viruses, too, that they can move back and forth between animal hosts and human hosts. Does the fact that coronavirus cells are able to do this as well? I'm thinking there's quite an interesting reservoir of white-tailed deer, for instance, in the United States that are infected with this virus. Does that also suggest that we are going to see? Is that also predictive of additional variants? You certainly raise that possibility with Omicron, for instance.

[00:44:35] **Rasmussen** Well, I'm so glad you asked that because that's actually something that my lab is looking at right now. But apart from the white-tailed deer, there is some evidence that some animals have been infected. There have been a number of case reports of zoo animals being infected, many big cats, things like that. Certainly, domestic cats are susceptible. It's thought that many small carnivores are susceptible, and certainly Omicron, as well as Alpha, Beta and Gamma are all naturally mouse adapted, rodent adapted as well. So, there's a number of candidate species, but honestly, we haven't really started to even scratch the surface of how many animals might actually be out there that are infected and that do have different variants, potentially animal specific variants of SARS-CoV-2 circulating in those population. But I think the white-tailed deer has been a big wake up call for everybody that animals that may or may not be perceived as even having that much human contact, although deer do have quite a bit of human contact, are in fact getting infected with SARS-CoVo2 derives from humans, and then it's continuing to circulate in those populations. What the impact will be on future evolutionary trajectory of

the virus with the impact will be on human public health, with the impact will be on animal health or one health as we talk about is really anybody's guess, but it's something we definitely need to look into more and my lab as well as others are starting to do just that.

[00:46:12] **Blum** Would I see another webinar in our future, right? Andres Biyani from Johannesburg, South Africa, is wondering about the effect of the anti-vax movement. He's specifically looking at vaccine resistance in South Africa on the trajectory of this variant. Not just vaccine and equity, but refusal to get vaccinated. And he wonders Kai specifically whether journalists are covering this in an adequate way and acknowledging the low rate of vaccinations in a country like South Africa as variants emerge.

[00:47:02] **Kupferschmidt** Oh, OK. I think that's one of those really, really tricky questions, I think. So, I think for me as a journalist, I've always tried to understand complexity and bring nuance to stories, it's not always easy, I'm very lucky I work at an outlet where I can do that, it's not always possible. And this is one of those examples. I don't have the background to know all the relevant information here, but it is one of those topics where really you have to look very, very closely at it because one of the some of the stories that I've seen either say, oh, look, this country, which has low vaccination rate and is a lower middle-income country actually throwing away these doses that it's got donated so why are we even sending them? Or there's so much vaccine hesitancy that makes no sense to even send the vaccine there. Yes, there's a lot of vaccine hesitancy in a lot of countries, and it's not all rich Western countries, and yes, some countries that are in desperate need of vaccine actually had to get rid of a lot of vaccines, partly for the reason that they were donated so close to their expiry date that it just wasn't realistic for them to use them in a vaccination drive. All of these things have a lot of reasons, and you can't just- the problem with these complex questions is that you can't just say, oh, look, there's vaccine hesitancy there, so then it doesn't make sense to even send anything there. The way that we have presented these vaccines, the way that we have distributed them unfairly so far, the way that we talk about these vaccines and the way that we talk about donating them, all of that matters and all of that plays into certain narratives. And certainly, the way that we dealt with the AstraZeneca vaccine, for instance, in parts of Europe where we decided it didn't, a lot of countries stop vaccinating their populations with the AstraZeneca vaccine and because they felt the risk benefit didn't make sense because they had other vaccines available that had a better risk benefit ratio. Now we then started sending these vaccines as donations to other countries and of course, that creates a narrative that you're basically giving what we consider a second-rate vaccine to other places. I want to be very clear that AstraZeneca vaccine provides a lot of protection, and especially where it matters, the T cells, when we're talking about protection from severe disease and death, it's really good. But we had these stories about the rare side effects that this vaccine cost and the way that we dealt with that you can't just take that out of the story and then say, oh, look, this vaccine hesitancy. It's one of those-I think there's this line in Cold Mountain where somebody said they make the weather and then they stand in the rain and say, it's raining. It's one of those situations to me where it is, you know, you do have to look at everything and the inequity itself, the way that we've dealt with it plays into this. And so, we should be trying to solve the supply side issue here. We should be making sure these vaccines are distributed equitably and then of course, there's also a challenge in most countries, including here in Germany, including in a lot of other countries, to actually convince people to take these vaccines and to explain to them why these vaccines are life-saving and really, really important. But you can't just take these little- you can't just take these things out of context and then try to argue with them that, for instance, it doesn't make sense to send these vaccines. I think that's been done sometimes. And the question sounded like it got at that a little bit. So, I just think that's not good journalism in a way.

[00:50:54] **Blum** And I have one very quick last question as we're about out of time. Unfortunately, that sums up some of the questions, it combines a bunch of questions I've seen, which is we've talked a lot about the evolution of the virus. But do we predict any kind of dramatic evolution of vaccines, vaccines against COVID-19 or SARS-CoV-2 that are more comprehensive, use different approaches? Protein based vaccines, for instance, that I don't think really got any traction this time around? Do you predict that we'll see vaccines evolving along with the virus?

[00:51:37] **Rasmussen** I mean, I certainly do. And granted, I need to disclose that I am a research scientist for the Vaccine Research Institute, but who is making a protein vaccine. But I do think that there's been a huge effort not only to develop new vaccines using the RNA technology, but there have been new protein technologies employed two as well as new adjuvants, a new production methods, things like that. There have been these I know virus vectors vectored vaccines as well, like AstraZeneca and Johnson & Johnson that are not new technologies, but they're new on the market anyways. And I think that there is a place for all of these vaccines. I think that what Kai just said is incredibly important because we can't be ranking this vaccine is better than the other one. All vaccines have some utility if they work at all. For example, these protein vaccines may not be useful for the primary series for everybody, but they certainly could be useful for boosters in the future and potentially as people continue to develop these technologies as we're past the pandemic and we move on. Maybe we do start using some of these vaccines, maybe they do have some advantages over the MRNA technology as we as we incorporate COVID-19 vaccines into the normal vaccination schedule, and then finally, there is a huge effort building on efforts that were already in place for influenza to make pan coronavirus vaccines. So I think that we'll be seeing all of these different vaccine technology platforms trying to develop those or at least vaccines that would protect potentially against all our Beco viruses of the stars like viruses. So I think that, you know, there's really a lot of things coming down the pipeline in terms of vaccines that will continue to improve and be more safe and more effective.

[00:53:32] **Blum** Thank you. That's really helpful. Kai, Purvi do you have any final thoughts? You been a fabulous panel. I have to say.

[00:53:43] **Kupferschmidt** Go ahead.

[00:53:44] **Parikh** Oh, no, no. I just I was just going to echo exactly what Angie said. It's actually exciting that there are so many different vaccine platforms understudy because we may find very well one works better as a booster than another one works better for a variant versus other and yeah, the pan coronavirus vaccines are very exciting, as well as some of these cold virus vaccines and protein subunits. But the one thing that I'm also very excited to see is the mucosal immunity vaccines that are being developed because, yes, maybe for an initial inoculation, this may not be ideal, but for a variant that loves the nasal pharyngeal passages like Omicron or whatever future holds, this may actually be a great option for a booster or to provide that extra inoculation.

[00:54:31] **Kupferschmidt** Maybe just, you know, as a nerd, I get super excited about all of these different approaches, and I think we're going to see a lot of this coming and that's really, really good. As a science journalist, what I've learned in this pandemic is that we already have really good tools. We're not using them nearly the way that we could be. And so I think whatever comes down the pipeline and whenever it comes, it is very clear to me that right now we really have to work on this fundamental problem of getting good

information to people about these vaccines that we have other vaccines that might come and really work to counter this polarization because I really worry even for the vaccines, but certainly for anything that's a coronavirus vaccine, this polarization is going to make it pretty much impossible to use these vaccines in the best way possible and to just get people to look at them in a way, in a rational way, in a way. And so that's I think for the next years, whatever tools we have in this pandemic, it's the saddest thing has been how badly we've used the tools we have already. So, I'm excited about any new tools coming. But please let us not pretend that when that tool comes in two years, it will magically solve anything. If anything, we could be if we don't do the work now, we're going to be in an even worse situation in terms of using these.

[00:55:59] **Blum** And on that happy note, I have just said fabulous. I enjoyed every minute of this conversation and I want to thank you for your time and all of the really interesting information you share. Thank you.

[00:56:14] **Parikh** Thank you so much, Deborah.