AMERICAN PUBLIC HEALTH ASSOCIATION

and

THE NATIONAL ACADEMY OF MEDICINE

+ + + + +

RESPONDING TO COVID-19: A SCIENCE-BASED APPROACH

+ + + + +

WEBINAR #18: COVID-19 CONVERSATIONS:
VARIANTS AND VACCINES

+ + + + +

WEDNESDAY
MARCH 17, 2021

+ + + + +

The webinar convened at 4:57 p.m. Eastern Daylight Time, Carlos del Rio, Moderator, presiding.

PRESENT
CARLOS DEL RIO, Emory University, Moderator
ANGELA L. RASMUSSEN, VIDO-InterVac, University of Saskatchewan; Center for Global Health and Security, Georgetown University
DAVID D. HO, Columbia University
MONICA GANDHI, University of California, San Francisco; San Francisco General Hospital

ALSO PRESENT
SUSAN L. POLAN, Associate Executive Director for Public Affairs, American Public Health Association

C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

4:57 p.m.

DR. POLAN: This webinar is entitled Variants and Vaccines. And it's good that you're all with us.

The webinar has been approved for 1.5 continuing education credits for CHES, CME, CNE, and CPH. None of the speakers have any relevant relationships to disclose through their work.

And if you want the continuing education credit, you should make sure to submit your first and last name. For the watch credit, they must have their own registration and watch today's event in its entirety.

All of the participants today will receive an email within a few days from cpd@confex.com, with information on claiming credit. All online evaluations must be submitted by April 27, 2021 to receive continuing education credit.

If you have questions or topics that you'd like us to address today or in future webinars, please email us at apha@apha.org.

If you experience technical difficulties during the webinar, please enter it into the Q&A, and someone will be in contact with you shortly. We will not be recognizing people who raise your hands. Please use the Q&A.

This webinar will be recorded. And the recording and transcript will be available on covid19conversations.org in the next couple of days, as well as more information on this series, recordings, and past webinars, will also be available at that same link.

It is now my great pleasure to introduce our moderator for today, Dr. Carlos del Rio. Dr. del Rio is a distinguished professor of medicine in the division of infectious diseases at Emory University School of Medicine, an Executive Associate Dean for Emory at Grading.

He's also a Professor of Global Health and Epidemiology at the Rollins School of Public Health, and the International Secretary of the National Academy of Medicine.

Dr. del Rio, over to you.

DR. DEL RIO: Thank you, Susan. I just

want to check, there's many comments coming in in the question and answer of people not getting audio.

Can somebody please type there, if they're now getting audio, or if there's any problem, because we need to solve that. Okay. So, the audio seems to be working. Thank you.

Well, thank you, Susan. And welcome everybody to today's webinar. Today we will be discussing some of the most critical issues being asked around COVID today, variants and vaccines.

What do we know about these new variants being discovered? And how will they impact the vaccines that we currently already use?

I'm privileged to be moderating this American Public Health Association and National Academy of Medicine COVID-19 Conversations webinar.

As we're moving from theory about vaccine distribution and allocation to actual practice, SARS-CoV-2 variants are quickly becoming more prevalent.

We will explore in this webinar the questions like what do we know about the variants? How do they emerge?

And what -- how are they impacting and how do we halt transmission? And will the current vaccine protect us against them?

I would like now to formally introduce today's presenters. We are joined by Dr. Angela Rasmussen, Dr. David Ho, and Dr. Monica Gandhi.

Angela Rasmussen used assistance biology techniques to interrogate the host response to viral infections. She has studied a huge range of viral pathogens from the common cold, rhinovirus, to Ebola virus, and the highly pathogenic avian influenza virus and SARS-CoV-2.

By combining current classical approaches to modeling infectious disease and pathogenesis with sequencing technology and machine learning, Dr. Rasmussen and her colleagues and collaborators have identified new host mechanisms by which viruses cause disease.

Dr. Rasmussen holds a Ph.D. in microbiology from Columbia University, and is currently an Associate Professor and Research Scientist at the Vaccine and Infectious Disease Organization International Vaccine Center at the

University of Saskatchewan. And an Affiliate at Georgetown Center for Global Health Science and Security.

Next is Dr. David Ho. Dr. Ho obtained his medical degree at Harvard University. And is currently a Professor of microbiology and immunology, the Clyde 56 and Helen Wu Professor of Medicine, and Director of the Aaron Diamond AIDS Research Center at Columbia University.

Dr. Ho has been studying in advancing therapies against viral diseases for nearly 40 years. He has been engaged in AIDS research since the beginning of the epidemic.

Dr. Ho's lab led the effort to develop a testing combination antiretroviral therapy that for the first time demonstrated durable control of HIV replication in patients. Dr. Ho's lab then focused on developing novel vaccines against HIV both in the laboratory and the clinic.

For the past decade, Dr. Ho's research in the field of HIV has been to develop strategies to prevent HIV transmission, including engineering especially important biospecific antibodies, and

developing a long-acting antiretroviral drugs as pre-exposed in prophylaxis. And to readdress a topic of HIV eradication.

Through the COVID-19 pandemic, Dr. Ho's previous experience as an advisor to the governments of Beijing, Hong Kong, and Taipei during 2002-2003 SARS epidemic led him to assemble a multi-disciplinary team of physicians, scientists and engineers at Columbia that has identified one of the broadest and most potent panel brand of antibodies against SARS-CoV-2 today.

Some of those antibodies are currently in clinical development for the treatment and prevention of COVID-19.

In addition to ongoing HIV research effort, the whole laboratory is continuing to investigate the pathogenesis and molecular mechanism underlying SARS-CoV-2 infection in order to bring new solutions to the testing, treatment, and prevention of COVID-19.

Last, but not least, is my good friend, Dr. Monica Gandhi. Dr. Gandhi is an infectious disease physician, and a Professor of medicine and

Associate Chief of the Division of HIV and Infectious Disease in Global Medicine at the University of California in San Francisco, where she's also the Director of the UCSF Center for AIDS Research, and the Medical Director of the HIV Clinic, Ward 86 at San Francisco General Hospital.

Dr. Gandhi's research focuses on HIV in women, and adherence specimens in HIV treatment and prevention. And most recently on efforts to mitigate the COVID-19 pandemic.

Through this webinar, we will be hearing from each one of them. And then we will have time for questions and answers from you in the audience.

So, just a quick reminder, if you have a question, please type it in the Q&A box. And we already have about 108 questions, so we're doing well.

So, Dr. Rasmussen, please kick off your -- the webinar with your talk.

DR. RASMUSSEN: Well, thank you so much, Dr. Del Rio. I think we can -- if we can advance to my slides. That's perfect.

Thank you so much. So, as Dr. del Rio

said, today -- I'm a virologist, and today I'm going to be talking about the virus side of things, and a little bit about the host side of things.

And you know, how this all -- how this all makes sense with regards to the COVID-19 pandemic. What does mutation really mean? Next slide, please. Oops.

Okay. I like to start all of my talks with a territorial acknowledgment and equity statement. Today I'm in Seattle. And I'm presenting from the unceded ancestral homelands of the Duwamish people.

I acknowledge and honor the First people of these territories and their Tribal government, their histories and ancestry, and their roles today in caring for these lands.

And I'd also like to acknowledge the long history of systemic inequity in academic science that has spanned centuries. My prior institution, Columbia University, and my current institution, Georgetown University, were both founded using profits from the trans-Atlantic slave trade and the sale of enslaved people.

And in addition, they excluded women and people of color from the academic community for more than 200 years, which has left a long and painful legacy of racial and gender-based inequality that continues to this day.

So, I encourage everybody watching this presentation today, to consider how you can contribute to making public health research a more equitable enterprise. Next slide, please.

So, I'm going to start by just giving a very basic primer on mutation and virus evolution. A lot of -- a lot of times this work on these variants is presented as something that's abnormal or alarming.

But, in reality, RNA viruses mutate all the time. And this is something that we can expect.

On the panel on the left is a diagram showing the relationship of genome-sized mutation rate. And as you can see, the higher eukaryotes, which includes people, other organisms, complex organisms that use DNA as their genetic material, have a much lower mutation rate and a much larger genome than RNA viruses like SARS-CoV-2.

Those have a very high mutation rate in part because the enzyme that copies the genome does not have proofreading capabilities.

And in addition to that, the genomes are smaller relatively compared to ours and compared to most DNA genomes. Which means that a mutation has a greater probability of having a functional impact.

And what this really means, is that when you have, on the left I've got a diagram of how this usually works. When you have a parental virus that gets into a cell that's susceptible to it and replicates, it will make many new progeny viruses.

Some of these will have the same genome copied faithfully from the parental virus. Some of these will have a mutation inserted randomly.

Some of those mutations may have no effect at all. Some of them may have a negative impact on the virus.

So, they maybe in a critical place that the virus needs in order to replicate and carry out its replication cycle.

This is referred to as a defective

interfering particle, or a mutant that has a defective genome. This would be under negative evolutionary selection.

Sometimes that mutation can occur in a place that gives the virus an advantage over the parental virus. Either it makes the virus more fit, it can replicate more efficiently, it can infect cells more efficiently, it can invade the host immune system more efficiently.

And this virus will be under positive evolutionary selection. That means after another round of replication, after these progeny virions go out and infect new cells, the mutant that has the advantageous mutation will quickly outcompete the older ancestral viruses and take over. Next slide, please.

So, as I said, this is a very normal process that we would expect to see occurring whenever viruses have the opportunity to replicate.

Unfortunately, SARS-CoV-2 has had many, many opportunities to replicate. As a result, there are many, many variants around the world.

And this is just a depiction of all the

different variants that have been observed by Nextstrain. And most of these variants will have really no functional impact.

But, as we're seeing now, variants have emerged that do have a functional impact that confers an advantage to the virus. And those are the ones I'm going to talk about today. Next slide, please.

So, this is a really nice diagram, I think, that The Economist made. It's not from a scientific journal, but I think it depicts this really well.

Early on, we had the lineage A. This was essentially the root of the pandemic, the original parental virus that first emerged in the human population. And then as that virus transmitted to new hosts, it began to diverge. We see some of those lineages going extinct, and effectively they're no longer circulating, such as the one from Seattle. We see others in the B lineage, which gave rise to all of the variants that we're talking about today.

And as it has continued to move through the human population, we've seen some mutations

such as the D614 gene mutation and the spike-protein becomes fixed, because it does offer a fitness advantage to the virus. It helps it replicate more. And that in turn has gone on to yield all of these sub-lineages, including the ones again, that we're talking about today.

Now again, many of these variants don't have any sort of functional impact. But many of them do. And that's what I'm going to focus on. Next slide, please.

So, this is the SARS-CoV-2 genome. The only reason I'm showing you this, is to show you that there is really quite a lot of genome here.

Even though this genome is really small relative to the human genome, it's still 30 thousand kilobases long. That is quite large for an RNA virus. And these mutations will be sprinkled throughout this genome. They occur randomly.

So even though a lot of the news coverage makes it sound as though the only mutations that occur occur within the spike protein or the receptor binding domain of the spike protein, they're actually scattered throughout this genome, both in the

structural proteins, spike envelope, membrane and nucleocapsid, nucleoprotein, as well as through the nonstructural proteins throughout the genome.

And these can have different effects. Some of them may have no effect. Some of them may have a functional impact. Again, the only ones that we've really studied in detail are the mutations in the spike protein. But there are others. Next slide, please.

And these are some of those. So, right now there are three well-studied variants of concern. And I should add that there really should be an asterisk on well-studied, or best-studied, because we've really only been looking at these for the past few months.

But as you can see, even though we've focused on the mutations that are in the spike protein because of the obvious implications for vaccines, there are these other mutations sprinkled throughout. Some of them are shared, which may suggest that they have a functional impact, although we don't currently know that. Next slide, please.

So, there are multiple mechanisms for

increased transmissibility. And that's why these variants are considered variants of concern, because there is a functional impact. And that has relevance for the pandemic.

Now, there are two main impacts that we need to be worried about. One is increased transmissibility, which I'm going to be talking about now. The other, I think, is going to be covered by Dr. Ho, and that is how this will impact vaccines over the long term.

But there are several possible mechanisms of the increased transmissibility. The first one, as I mentioned before, is increased fitness. So, this means that basically the virus is replicating more efficiently. It's producing more infectious viruses. It's shedding potentially more infectious viruses. There's just more virus being produced. This can result in increased viral shedding or potentially also a longer interval of contagiousness.

Receptor binding affinity is another mechanism of increased transmissibility. This basically allows the spike protein to bind to the

ACE2 receptor more efficiently. This could potentially decrease the number of virus particles that you need to be exposed to in order to establish a productive infection. This results in increased infectivity.

Another possibility is increased virion stability. We don't have a lot of evidence that that's the case for any of these variants, but this would mean that the virus can basically remain infectious in the environment for a longer period of time.

And then there's the last possibility, which is immune evasion. And while that largely will be covered by Dr. Ho as I mentioned --

(Audio interference.)

-- although this could also explain some of the increased transmissibility that we're seeing, specifically with regard to reinfections.

So immune evasion can mean a lot of different things. It can mean the ability to circumvent antibody neutralization, which is what we've heard a lot about. But it can also mean other things that contribute to viral fitness, such as

the ability to invade the host and make antiviral immune system, the interferon response.

Some viruses also can antagonize adaptive responses, or other immune cell effectors, such as macrophages, and modulate the type of cytokines they're producing, modulate receptor expression, things like that.

So, immune evasion can take a lot of different forms. But, in some ways, it can also increase viral fitness. It can make hosts more susceptible. It can make people more susceptible to having more severe disease. Next slide, please.

So, I'm going to talk a little bit, before I finish up, about the impact of immune evasion on transmission specifically. And, as I mentioned before, a lot of attention has been paid to the effect of antibody neutralization.

So, mutations that are in the receptor binding domain and the spike protein, are also thought to potentially effect the binding of important antibodies that will neutralize the virus or render it noninfectious.

The reason why the receptor binding

domain is such a hot spot for these neutralizing antibodies, is that that's actually the part of the spike protein that interfaces directly with ACE2.

If those proteins are changed, or those epitopes that the antibodies bind to, the antibodies may not bind to that anymore, and will no longer block the interaction between spike and ACE2, allowing the virus to continue to infect -- to infect new hosts.

And this has been observed in Brazil with the P.1 variants. There's been a lot of concern about the E484K, or EK mutation in the receptor binding domain of spike.

And that's been attributed to the rise in cases, despite the fact that many people in Manaus, Brazil have already been infected and have natural immunity to SARS-CoV-2 infection.

We're still seeing cases going up, which might suggest that people are being reinfected. And it maybe because this P.1 variant has emerged, which can get around this antibody neutralization.

Next slide, please.

But, as I said before, antibody neutralization via the receptor binding domain, isn't everything. It's not -- it's not the sole determinant of whether a virus will be able to establish a productive infection in a new host.

And it's not the sole correlate of immune protection either. Right now we don't know a lot about the true correlative protection.

Obviously neutralizing the antibodies are important. But, there are other non-neutralizing antibodies that can also be protective.

There are T cells. There are other aspects of the immune system that can be in play here. And we really don't know much about how these variants are impacting that.

So, on the left upper panel here, we have a diagram of various pseudovirus neutralization assays that have been carried out.

And this just really shows the different variants that have emerged, and how well antibodies to the ancestral SARS-CoV-2 isolates will neutralize them in a pseudovirus assay.

Now, a pseudovirus assay, it should be pointed out, is not actually measuring neutralization of infectious SARS-CoV-2, it's using a surrogate virus to evaluate how well those antibodies neutralize. So, it really should be taken with a grain of salt.

But, we can see here, there is a gradient in people who've been vaccinated, with the ability of their antibodies to neutralize these different variants with the P.1 and B.1.351 variants discovered in South Africa, being at the lower end of neutralization.

Again, this may explain some of the reinfections we've seen. However, we've also seen, and the panel below that shows this, that antibodies against the ancestral spike protein can still neutralize all of these variants to different degrees.

Part of this is the polyclonal nature of the immune response. So, it's not just one antibody or one neutralizing epitope that's going to be important. It's going to be the totality of those immune responses.

So, it's not always clear looking at these types of neutralization assays. And this is with -- this neutralization assay depicted here, is actually with SARS, infectious SARS-CoV-2.

It's very difficult to say just looking at these neutralization experiments, what effect that's going to have meaningfully in the population in terms of vaccines or prior immunity ability to stop transmission of the virus.

And then just this top, this top spike protein as depicted here. This is a ribbon diagram of the spike protein binding ACE2.

And what I'd like to point out is that this N-terminal domain, or NTD, is also thought to be important for neutralization. And some of these variants do have mutations in the N-terminal domain.

Those are depicted here in yellow. Those may also play a part in determining whether somebody who is exposed to a variant, if they have antibodies to a prior virus, you know, that will determine whether they are going to be able to be infected with that virus, and also to transmit it to others.

So, there is still some big remaining questions. And that is, how much this prior immunity, whether that be from vaccines, or from being convalescent and recovering from COVID-19, provide actual sterilizing protection.

How can that protect you from infection? And in turn, be able to protect you from being able to transmit the virus to others.

And what impact does this have on viral shedding? Because again, even if you can get infected because you may not have as good antibody neutralization, does that mean that you're still going to be shedding virus?

As I mentioned, there are other mechanisms that take place after entry, such as the interferon system, such as T-cells, and other parts of the immune system that will have an impact on that. We don't really know.

And what is the overall impact going to be on transmission at the population level? And that's a question that I think is foremost on everybody's mind. And that is being addressed right now by the various experiments that are going on.

And I believe this is coming to the end. I think there's one more slide. Oh no, sorry, there's two more slides.

This is just a summary of the three variants again, that are quote/unquote, best studied at this point. And we can see here that the B.1.1.7 variant from the U.K. does have a demonstrable increased transmissibility. It also has increased lethality, potentially, judging by multiple studies now that show a greater risk for hospitalization and death when you're infected with this variant. However, it does not seem to evade immunity very well.

B.1.351 doesn't actually seem to be more transmissible, but again, it maybe just because it does have this EK mutation, as well as several as well as several other mutations that seem to be important in terms of antibody neutralization.

And it's really not known very well what the effect is going to be for the P.1 variant.

I look forward to hearing about some of the other variants, including the B.1.529 variant from Dr. Ho next. So, next slide, please.

This is just my disclosures of conflicts of interest. I'm happy to have a longer discussion about this topic in the Q&A section.

DR. DEL RIO: Thank you, Angie. That was fabulous. So now, David, why don't you take it from here?

DR. HO: Okay. Thank you, Carlos. Could I have my slides, please? I am showing you the same artist's rendition of the family tree of SARS coronaviruses. And could you push the next slide?

I'm going to first talk about the U.K. variant as well as the next South African variant, based on work that we started doing in December as these new viruses were described. Next, please.

And then I will say something about the variant P.1 from Brazil. And finally, I will end up with the variant that we uncovered last month here in New York.

So, the first part is already published online. So, I will go over it very quickly.

On the upper left you see the alignment of the spike gene, and spike protein, and with the

various mutation marked for the South African variant or the U.K. variant.

And you see a cluster of mutations in the N-terminal domain, as well as Q mutations in the receptor binding domain. And there's almost always a Q mutation near the so called furin cleavage site.

And we -- when we saw these mutations reported in December, we actually already had seen some of those mutations before in the viruses that we had been studying in the laboratory.

And in fact, four or five of them were identical. And those viruses were generated by putting monoclonal antibody pressure on SARS-CoV-2, and see how the virus evade.

So, upon seeing these new sequences, we actually thought that these were largely escaping from antibodies in vivo.

And so, we started to characterize these variants in terms of how they might be resistant to monoclonal antibodies.

So, we studied a total of about 30 monoclonals. Some of which are shown in this slide.

On the left, bottom left, you'll see we had monoclonal antibodies that are directed to the N-terminal domain.

And in fact, most N-terminal domain antibodies are directed to a single super shaded in yellow. And you can see they all neutralize the wild-type virus, shown in black.

But again, B.1.1.7 first identified in the U.K., the viruses are, the virus is resistant, completely or largely to these monoclonal antibodies.

And similarly for B.1.351 first identified in South Africa. It's pretty much the same pattern.

However, these N- -- so-called N-terminal domain antibodies are not in the clinic at this point. So, it's clinically not relevant at this time point.

But on the right, are a panel of antibodies directed to the so-called receptor binding domain of spike.

And on the top, you see the trimer structure with the top view. And you can see the

portion that is responsible for binding to their receptor, is shaded in yellow with the second graph, second structure there.

And then -- and then there's the two side views. The inner side view and the outer side view.

And we stratified the monoclonals according to the epitopes. And those are traced out in the various color lines.

And to make a long story short, is that if the monoclonals target the inner side or the outer side, they generally retain activity against the variants shown in magenta and orange.

However, when you move to the center, the so-called receptor binding motif, you can see the yellow -- the orange line is essentially flat, or largely flat.

And that suggests that antibodies direct at the very top of the receptor binding domains no longer work well against the B.1.351 variant.

And importantly, several of these antibodies are already authorized for emergency use to treat patients. And I'll come back to that

point in a second. Next slide, please.

And so the fold change in the antibody resistance, is expressed on the left in this heat map table. And I won't go through the NTD mutations again, because those are not antibodies that are in the clinic.

But, we mapped the mutations that conferred the resistance to the antibodies based on the pseudovirus system.

But, if you'll focus on B.1.351 with the yellow arrow on the bottom, and look at the antibodies that are not working against this variant, you see those that are recognizing the receptor binding motif in the middle.

And that level of resistance is largely inferred. If you look down to E484K, you can see a bunch of red boxes there, suggesting that that resistance is largely conferred by a single mutation.

And that's the E484K that Dr. Rasmussen mentioned, and I will continue to discuss. Next slide, please.

And so, in terms of looking at antibodies that are either receiving EUAs, or those that are

in active clinical development, you can see, let's just focus on the left and looking at neutralization of the authentic virus.

You can see the blue and green lines dropping out. That shows you the validity of LY-55, the validity combination, no longer work against the B.1.35 variant.

And in fact, the B.1.35 variant impairs the activity of several other monoclonal antibodies, some of which are already in clinical use. So this is a -- this particular variant is very relevant for clinical practice. Next slide, please.

Next, we turn our attention to convalescent plasma collected last spring from people infected with the virus resembling the original strain, and looked at the impact of these two variants on the neutralizing activities of the convalescent plasma.

And the wild type is shown in the middle. And the B.1.1.7 from the U.K. is shown on the left. And the B.1.351 on the right.

And you can see, there's not much effect with the B.1.1.7 variant. However, against B.1.351,

there's a 9.4 drop in neutralizing titer.

And that raises a specter that this low, this may lower protection against reinfection, and as we reported these results. Next slide.

We immediately recognized that Novavax, in their trial in South Africa, had a number of placebo patients who were previously infected.

And in that study, they showed that when confronted with the new B.1.351 variant, there was no protection against reinfection.

And then, of course, the story that Dr. Rasmussen just covered in Manaus, Brazil, you could see on this slide, in the spring of last year, they suffered a huge wave of outbreak due to SARS-CoV-2, presumably from the original virus.

And then by late -- by November, much of the population, 76 percent of the population was already seropositive. And yet in November/ December with the emergence of the P.1 lineage, you could see Manaus undergoing a second larger wave of outbreak.

Suggesting that there's very little protection against reinfection due to the P.1. virus.

Next slide, please.

We also turned our attention to looking at sera collected from individuals vaccinated with Moderna or Pfizer vaccine. These were taken from after this, about two weeks after the second shot.

And once again, we compared the neutralization activity against the variants versus the wild type virus. And you could see the magenta and black dots are approximately at the same level, suggesting not much of an impact on mediated by the B.1.1.7 variant.

However, you see on the right, with the orange dots, a 10 to 12 fold decline in neutralizing activity against this authentic virus.

And this, at the time we generated these results, we actually wrote that it may compromise vaccine efficacy.

And indeed, one week later, next slide, please, Novavax reported their findings with their vaccine, demonstrating 96 percent efficacy against wild type virus.

And slightly or similar efficacy against B.1.1.7. However, in South Africa, against B.1.351,

the efficacy was only 49 percent.

And one day after that report, next slide, please, J&J reported their data, stratified differently. In the U.S. the protective efficacy was 72 percent, and only 57 percent in South Africa.

And you may have seen the report get out in the New England Journal this week, that AstraZeneca vaccine in South Africa has demonstrated an efficacy of only 10 percent against the B.1.351 variant when the efficacy against previous variant, or previous viruses was well over 70 percent. Next, please.

So, more recently we turn our attention to the P.1 variant from Brazil, and the sequence changes as shown on the left, comparing with the U.K. and South African variant.

And you can see that the Bra -- the P.1 shares the same three receptor binding domain mutations as the South African variant. However, the NTD mutations are quite different.

And then if you come to the right panel, let's just focus on the antibodies under RBD with EUA.

And you can see of the four anti -- monoclonal antibodies therapeutics that have received emergency use authorization, one is unaffected, whereas three are inactive or impaired.

And that has obviously ramifications for clinical practice, as these antibodies are now being administered at various infusion centers. If you now look at the convalescent plasma, there's a 6.5 fold decline in activity against P.1. And the vaccine sera, the decline is much more modest, ranging from 2.2 to 2.8 fold.

And this is interesting, because the RBD mutations are virtually identical to those found in B.1.351.

And so, it's suggestive evidence that the NTD mutations, in fact, have tremendous impact. Next slide, please.

So, we -- as we were doing these analysis, we said, you know, if the U.S. has more cases than other countries, certainly we have variants.

And we also wanted to know whether the variants from abroad had made it to our city. So, we started to look into the biobank at Columbia

University Medical Center.

And we started this process by probing for 501 mutation as well as the 484K mutation. And the panel on the left simply showed that we noticed these variants first in November, but only a couple of cases.

And then a few more cases in December. But starting in January, we saw a very dramatic and alarming rise in variants, particularly variants carrying the 484K mutation.

And of course, these were then subjected to whole-genome sequencing. And what we've noticed over the ensuing months is that, if you look at the panel on the right, the variant with the 484K has been rising.

And next slide, please. And in fact, over the past week or so, it's now up to 36 percent.

So, but to our surprise, next slide, please, when all these were sequenced, we found in the -- some cases of B.1.1.7 from the U.K., P.2 from Brazil, B.1.351 -- one case of B.1.351 from South Africa.

But, in fact among our collection, were

a huge cluster of viruses that fell into the lineage of B.1.526. So, it's apparently a home-grown variant carrying the E484K mutation. Next slide, please.

Next please.

(Long pause, no response)

DR. DEL RIO: Can we have the next slide, please?

(No response)

DR. POLAN: I think we -- Dr. Ho was, we've lost the connection.

DR. DEL RIO: Okay. I think we lost Dr. Ho. So, let us -- this was his last slide.

And basically, I mean, showing very clearly that the B.1.1.7 variant, the so-called U.K. variant becoming the dominant in most parts of the U.S. But, it's being out competed by the B.1.526 in New York City.

And you can see that very clearly here how, you know, in California and Florida, those are the two variants that are -- that are taking over.

And the CDC has told us that by March

23, this will likely be the most common variant in the United States.

But, look at New York, we're seeing that's something very different, and which has a very different variant has taken over.

So, again, I think what we need to -- lessons out of this is that sequencing is critically important.

So, can we have the next slide, please? We're going to move on now to Dr. Gandhi.

Monica will bring it home for us. As clinicians, as public health practitioners, what does this all mean for all of us?

So Monica, take it from here.

DR. GANDHI: Okay, great, thanks. I am going to talk to you about kind of the clinical implications of the vaccines as a clinician, and it's become specifically also the CDC guidance to clinical practice. Next slide.

So, I do want to remind us, of course, as we've been talking about in this session, that immunity is not just antibodies, and essentially, as you know, there's two types of immunity.

There's antibodies that come from plasma cells and then there's T cell immunity, and we think a lot about T cell immunity in HIV because the virus itself, the HIV virus itself infects CD4 cells, and of T cell immunity, there's two types, two flavors.

There's CD8, which are cytotoxic killer T cells and then there's CD4 cells which are essentially what you want for immunity and enduring immunity against viruses is you want specifically Th1-tilted CD4 cells.

And so the reason I'm telling you this is that the vaccine trials luckily, unlike other vaccine trials that weren't done in this era of high technology where we can measure T cells, actually looked at CD8 and Th1 CD4 cell responses against viruses, which was great because we have some confidence about the generation of a very robust T cell response from the different vaccines. So, next slide, please?

And the reason that I'm just going to -- this is a very busy slide, but the reason I told you about the immune system is I want to stress

to you about this question of what did they measure in the vaccine trials?

So, let's look at essentially there are nine vaccines in the world at this point. Three that are not on this list, on this table are Sinopharm, Sinovac, and the Covaxin vaccine. Those are in -- the first two are in China. The last one is native to India.

And that's because they didn't measure some of these T cell responses and they're only in press release form, so I'm waiting for more data on these, but let me tell you about the six vaccines for which we have phase III clinical trial data.

And the Moderna and Pfizer, we have publications on. The Johnson & Johnson, we still have the FDA report, still waiting on a peer reviewed publication there. AstraZeneca has a publication. Novavax is still a press release, but updated last week, and then the Sputnik is in a Lancet publication.

So, if we concentrate on the top three here that led to the CDC guidelines for example, what we have authorized in the U.S., you can see that -- well, actually concentrate on all of them

and then we'll go back to the ones in the U.S.

The one thing I want to point out is essentially the column that's shaded yellow, which is that all of these vaccines give a very high protection from severe disease, and actually there was only one person that was hospitalized in the Moderna trial who got the vaccine after two doses who needed hospitalization from COVID.

Otherwise, all of the hospitalizations and deaths that were related to COVID occurred in the placebo arms, those who got the saline shot, and that is across all of the vaccines, including Novavax across the world and in South Africa, and including AstraZeneca actually in the UK trial and the phase 2B study in South Africa, and there were about 15 severe cases in the AstraZeneca 2B South Africa trial and the UK trial.

So, all of the severe disease, luckily all of these vaccines look like they're protecting us from severe disease, which I'll get back to when we go back to T cells in the next slide.

So, let's focus on the top three vaccines, the ones that are authorized in the United States.

The Moderna vaccine is an mRNA vaccine, quite innovative, where the mRNA genetic material is put inside this lipid nanoparticle and injected, the first time that we've had these for pathogens, at least in widespread use.

There have been some tumor vaccines using this technology, and this technology has been developed over time, but this is the first time we're using it for a pathogen in humans in widespread use. So, Moderna is an mRNA vaccine and so is Pfizer.

And then the Johnson & Johnson vaccine, I wouldn't say is a typical vaccine, but it is one that's been used more, for example, in Ebola vaccines. This is an adenovirus shell, so a non-replicating cold virus, adenovirus, in this case a human adenovirus, but it doesn't replicate in your body, and it contains the DNA.

And all three of these vaccines contain the mRNA or the DNA to code for the spike protein that you've heard so much about and the receptor binding domain, so it's actually the genetic material coding for that protein.

The genetic material is injected in these

different formats and then your body itself essentially translates into protein, the spike protein, the receptor binding domain, and then you raise an antibody response and a T cell response.

The Moderna is two shots every four weeks apart. Pfizer is two shots every three weeks and that's it. Johnson & Johnson is one shot so far in the ENSEMBLE trial.

And this is the important part. It is column four. I want to really point out to you that they raised neutralizing antibodies that were measured in all of the phase I and II trials of these three vaccines, but they also raised really strong Th1-directed CD4 cell responses and CD8 cytotoxic killer cell responses.

In addition, all three of them, and actually all of them, they looked at in macaques primate models, and after they gave macaques the vaccine and gave them back the virus, they were unable to replicate it in their noses or anywhere else.

So, it is very important to say that these T cell responses look like they were generated

in a really strong manner. That's true in AstraZeneca and Novavax, and also in the Sputnik trial.

There was large numbers of people who got the vaccine, so you can assume that an equal number got the placebo shot, mostly saline, and that's listed in column five.

And the Johnson & Johnson notably was performed in the U.S., Latin America, and South Africa at a time where variants were circulating in the sense that in South Africa, 95 percent of the virus that they sequenced was the B.1.351.

And in Latin America, it was sort of a mixture essentially. I'll make it simple. In Brazil, it was a P.2-P.1 mutant variant. Sixty-nine percent of the strains circulating at the time, during the time of trial, were variants.

Again, I tell you that the protection from hospitalization was near complete, so the outcomes that were severe, which we break down in the second to last column, mostly occurred in the placebo arms. So, if you got vaccine, you were very unlikely to get severe disease.

So, again, there was one person who was hospitalized in the Moderna trial. That wasn't in the paper, but the FDA adjudicated that there was one percent who got vaccine who did need hospitalization for COVID.

Otherwise, all of the hospitalizations for COVID that occurred in the Moderna, the Johnson & Johnson, and the Pfizer study, and naturally all of them down the line, AstraZeneca, Novavax, and Sputnik, all in people who got the saline shot, so severe disease was very protective.

And then the very ability in the outcomes really occurred in that final column, which we were talking about with Dr. Rasmussen's and Dr. Ho's talk about antibodies, the variability against, and efficacy really occurred against more mild disease.

So, let's take the Modern and Pfizer. They were actually almost 100 percent effective against severe disease, but they were 94 and 95 percent protective against mild disease, which is still pretty good, and then the Johnson & Johnson, which was again conducted at a time, the trial,

when variants were circulating, 72 percent efficacy in the U.S., 61 percent in Latin America, and 64 percent in South Africa.

And the same findings were seen for the other three down below, not Sputnik, which was only studied in a particular region, but AstraZeneca, same thing, not as effective against mild disease as it was against severe disease, and the same thing with Novavax. We just got the results last week.

There were ten severe cases in the UK and South Africa, and they were all in people who got the placebo or the saline shot, so really good efficacy for all of these. This is clearly the right modality to choose, which is the spike protein and the RBD, against severe disease. Next slide, please?

Why are these so effective against severe disease? Really, we do have to remember our T cell responses and these CD4, Th1, and CD8 cell responses. T cell responses do modulate the severity of disease.

There's a very nice paper up on the right

corner of this slide that looked at highly functional, virus-specific, cellular immune responses in people who get asymptomatic SARS-CoV-2.

What is that mystery besides host susceptibility? What is it about your immune system that you can get asymptomatic disease which is very common with SARS-CoV-2 versus symptomatic?

And one of those features of you as a host is your ability to mount a strong T cell response or cellular remediated immunity, and so people who are asymptomatic are more likely to have highly functional T cell responses.

T cell responses do modulate the severity of disease. They also last a long time. There's been studies after measles vaccination 34 years later that you still have strong T cell responses, same with SARS-CoV, which is the first SARS pandemic in 2002-2003.

T cell response is preserved in PBMC 17 years later, and I think it is that T cell response in all of these six trials that I showed you that seemed to have led to this protection against severe disease.

Even prior to vaccines, data were indicating that cross T cell immunity from other coronaviruses led to more mild SARS-CoV-2 infection.

This could be explaining some of our more milder outcomes in countries like India, and if you get reinfected after natural infection or vaccine, which hopefully will be rare, it should be more mild if you've mounted a good T cell response to your vaccine.

There is a nice paper that I always want to refer people to from the 1918 influenza pandemic survivors. This is a paper in Nature where 90 years later, they took three years olds who had been exposed to the 1918 pandemic, and this is on the top left corner of that previous slide in Nature, and they had been three in 1918, and now 90 years later, they still had strong memory B cell immunity and that could be stimulated to produce neutralizing antibody against the 1918 influenza strain. Next slide?

I do want to give you just a couple of details on the three main vaccine trials that got

authorization in the United States only to remind you of the demographics of the studies, to remind us that they weren't only enrolling people who are perfectly young and healthy.

There was an attempt to get people who are older or had comorbidities in this trial, and we think a lot about this in HIV. You want representation in your trial.

So, again, the Pfizer is, this was published in the New England Journal, two shots, 30 micrograms, three weeks apart, and of the 38,000 or so reported on in this and how many outcomes they had in the New England Journal study, about half were female, 82.9 percent were white, 9.8 percent were African American, but at least 28 percent were Hispanic or Latinx, so more diversity in this population, at least of that representation.

Twenty-one percent were over 65 years old, so more susceptible to severe disease. The median age was 51. And there was representation of comorbidities that could predispose to severe disease, obesity in 35 percent, diabetes, some, pulmonary disease, some.

And as I told you before, again of the 170 people who had symptomatic COVID, meaning they said they didn't feel well, that was the outcome and they got swabbed, 162 of those were in the placebo arm, so only eight people got COVID in this huge vaccine trial and they were all mild disease in at least the Pfizer trial. All of the people who got severe disease were in the placebo arm. Next slide?

In the Moderna trial, a similar attempt at least to get more diversity among trial participants. This was 30,000 people. They were all 18 years of age or older, by the way. Pfizer was greater than 16, so it is approved down to 16 years old.

Two shots, 100 micrograms, four weeks apart, and this was almost 50 percent female at least. Twenty-five percent were over 65 years old and 36.5 were participants from communities of color.

And then there was this high-risk community, meaning 22 percent had some comorbidity that made them more at high risk. The mean BMI actually was 29.3, so it wasn't a low-risk population

necessarily, which is good for our diversity in clinical trials.

There were 196 final total symptomatic infections, again the majority, most of those, 94 percent of those were in people who got the salt shot and only 11 were in the vaccine group, and as I told you, 30 cases of severe disease.

All of those were actually in the placebo shot. The one got adjudicated later and there was one additional severe disease in someone who got the vaccine. They did do fine. Next slide.

And then finally the Johnson & Johnson vaccine, the third that we have authorized in this country. It was also a large trial, 44,000 people.

It was again enrolling across South Africa, Latin America, and the U.S., 468 cases of symptomatic COVID, seven deaths, 16 hospitalizations, sorry, that's a typo, and all of those were again in those who were in the placebo arm, none in the vaccine arm.

There were some people who had severe disease, but they actually stayed at home. They

didn't need medical attention, and it was equally effective against people who didn't need medical attention and stayed at home, again across all of the variants.

It was 85.4 percent effective against in Latin America, South Africa, and the U.S., and then the difference was in moderate or mild disease as I already told you in the previous slide.

Interestingly, the immunogenicity data from the New England Journal phase I/II study of Johnson & Johnson shows that the antibodies are going up over time, and hopefully our T cells are too.

So, hopefully we're going to see more efficacy or effectiveness of the Johnson & Johnson vaccine in the real world as we rate past four weeks, because remember, the phase III trial only adjudicated outcomes at zero to 14 and 15 to 28 days.

By the way, outcomes were better at 15 to 28 days than they were in zero to 14 days. So, hopefully after 28 days, we're going to even see better outcomes with the one-dose Johnson & Johnson,

and there is a two-dose trial in progress, the ENSEMBLE 2 trial. Next slide?

The next question that's very important clinically for us who are clinicians and seeing patients and advising them about what to do after vaccination is will vaccines help transmission? At least for the SARS-CoV-2 vaccines, I think there's four biological reasons why we think they will reduce transmission.

Number one is that IgG, which is stimulated very well by all of these vaccine trials, does actually enter the nasal mucosa. Immunoglobulins are not sitting in only their compartments. So, IgG, which is a systemic immunoglobulin, does go into the nasal mucosa as seen in other studies that look at antibodies and mucosal defense.

Number two, systemic vaccines do induce IgA responses. IgAs are immunoglobulins that protect us more in the nasal mucosal level.

Not only do we know that from other parenteral-administered vaccinations, not nasal-administered, but administered by injection

as shown here on the top study, but also there was a very nice study from SARS-CoV-2 vaccination last week that the administration of the mRNA vaccines produce plasmablasts and produce very high levels of IgA, which will hopefully protect us in the nasal mucosa.

The third biological plausibility reason why these vaccines are going to stop transmission is because monoclonal antibodies that we give as outpatient treatment also hasten clearance from the upper respiratory tract as well as the lower respiratory tract.

And then the fourth reason is that because in macaques, we actually know that when they gave the vaccine and then actually afterwards rechallenged them, there was no ability to reproduce in the upper airways. Next slide?

So, are these vaccines working? These vaccines are working. This is a paper and a press release that was one year after the declaration of the WHO pandemic on March 11, 2021 that Pfizer released from real-world data in Israel.

This shows that 94 percent of

asymptomatic infection is being prevented by these vaccines. If they are 97 percent effective against symptomatic, hospitalizations, severe, deaths, that's the same efficacy that we saw in the clinical trials. That's amazing when you see effectiveness equal efficacy.

Unvaccinated individuals are the ones that are in the hospital with COVID-19 right now, but vaccinated people seem to be safe and very safe from hospitalizations and severe disease, and of course that rollout was occurring during the circulation of the B.1.1.7 variant. Eighty percent of the circulating virus in Israel during the rollout of the Pfizer vaccine was B.1.1.7. Next slide?

This is another study that looks at this question of mRNA vaccinations preventing asymptomatic infection. This was a study published in CID last week about swabbing in the Mayo Clinic system patients before they go in for surgery. We always swab them to make sure that they are not infected with COVID to keep the physicians safe.

And the risk of asymptomatic infection

was 80 percent lower after even just one dose of the mRNA vaccines, either Moderna or Pfizer, and still after two doses, than compared to those who were unvaccinated.

So, for sure, we're definitely getting evidence as expected that symptomatic and asymptomatic infection is reduced by vaccines. Next slide?

This slide actually shows you all of the studies that have shown this. Again, the clinical trials were not designed to show us whether asymptomatic infection was reduced. That wasn't the design of the trials, but we're getting great real-world data.

The top study is from healthcare workers in England. The next one is healthcare workers in Israel. The third is patients in the Mayo Clinic health system, which I told you about.

The next study is a New England Journal study from the rollout of the Pfizer vaccine. Second to last is the pre-surgical patients in Mayo Clinic that I also told you about, and then healthcare workers across Cambridge.

All of these are showing a reduction after vaccination in asymptomatic infection. So, do I think that vaccines will stop transmission? Yes, I do, and I think that our real-world data is absolutely pointing us in that direction.

Importantly, and it's cut off at the bottom, there are two papers that show that even after you've been exposed and you get some virus in your nose, that your viral loads are very low, and there are two papers that show that the viral loads are so low in your nose afterwards, we'd still need to do a culture to see if they're even infectious. Next slide?

The real-world data is amazing on these vaccines, which is going to lead to why I tell you about the CDC guidelines and why we're so excited about these vaccines.

This is just data that was presented this week, again out of Israel, but it's a really nice figure, that among those who are vaccinated in Israel, which is, of course, everyone over 60 at this point, that is the plummet that you see in hospitalizations.

Hardly anyone who is over 60 is getting hospitalized for COVID-19 because of the high vaccine administration in that population. So, those two figures are showing a very nice result and we're seeing the same data from here in the U.S.

Long-term care facilities were targeted first for vaccination and so were healthcare workers, and you can see this massive reduction in cases and deaths, and this is actually cases, but the same is true, of course, of hospitalizations and deaths.

This is data up to just two days ago in the long-term care facilities here in the U.S. showing really a massive reduction in cases with mass vaccination. Next slide?

Will vaccines work against variants? It depends on the T cell response. Next slide? I do want to remind us that the T cell response is very robust against natural infection.

This is a paper from Cell with natural infection showing a very broad T cell repertoire across CD4 epitopes and CD8 epitopes after infection, and so hopefully if there is a reinfection, it will

be mild if you have a robust T cell response with your vaccination.

And then the next slide shows you a nice paper that illustrates that after vaccination, that they've looked at SARS-CoV-2 specific CD4 and CD8 T cell responses after those people who had gotten vaccinated, and they compared -- and after they had gotten vaccinated or had natural infection, looked at T cell responses against different variants.

There was B.1.1.7, B.1.351, P.1, and CAL.20C, and there was no difference seen at least in the T cell response against these variants in vaccinated blood from the mRNA vaccines, so I think that's really hopeful in terms of our protection against severe disease in the future from variants. Next slide?

So, I think this is why I'm not worrying as much clinically, at least in terms of variants. This is like Dr. Rasmussen and Dr. Ho pointed out. This is what RNA viruses do. SARS-CoV-2 actually does not mutate that fast. It mutates quite slowly compared to influenza. It was just transmitting

a lot.

And the T cell responses is what I'm focusing on, at least in terms of being a clinician and being concerned about hospitalization of severe disease, what we're seeing in the hospital.

And mRNA vaccines and DNA vaccines certainly can be tweaked or changed, as they are being actually from companies to code for new variant boosters in the future if required. Next slide?

So, this leads us to where the CDC guidelines are. Certainly we want to tamp down transmission right now as we are increasing vaccine rollout. This is why we are keeping restrictions in place as we are rolling out the vaccines, and we're not rolling them out as fast as the UK.

Actually, there was a Scotland study yesterday that just showed that with one dose of the AstraZeneca, there was a 94 percent reduction in hospitalizations across Scotland, again a place where there's circulating variants, at least B.1.1.7, with the AstraZeneca.

So, we're not rolling it out as fast as they are there, and we need to keep our restrictions

on and peel them off slowly as we administer vaccines. Next slide?

However, we also want to motivate vaccines. We want to motivate all of this optimism. These are amazing vaccines. I just told you a story of vaccines that we did not think they were going to be this effective and it's time to start motivating optimism.

And, in fact, I think vaccine optimism can reduce vaccine hesitancy. I think the public is very savvy. They can understand tiered messaging. If you're vaccinated, what do you do? If you're unvaccinated, what do you do?

And I don't believe in a philosophy of giving an inch, they'll take a mile. I don't think that's appropriate, at least from my experience with harm reduction in HIV.

And so what did the CDC say on March 8? Vaccinated and vaccinated people can feel free to mingle with each other without restrictions.

And importantly, and this has implications for us as clinicians, there's no need to quarantine if you're exposed after vaccination

if you have no symptoms. So, if you don't have symptoms and you got exposed, you can actually go to work the next day. That is quite a change once you are vaccinated.

If you are vaccinated around unvaccinated, it depends on the situation. If you are going into a home, for example, or a small gathering where there are unvaccinated people who are low susceptibility, the CDC is acknowledging all of this data on reducing transmission and saying, yes, if you go into a home and there's a grandchild, for example, who is unvaccinated, it's fine to be around them without masks and distancing.

Of course, in public, we're going to keep our social norms and we're going to keep masks and distancing until we have reached more vaccination, and unvaccinated around unvaccinated, keep all of the usual restrictions.

And that's where we are with the CDC guidelines. I think they're appropriate. Next slide, please?

And I think that again, I want to message optimism as a clinician. This is some messages

from Europe, who actually aren't doing a good job with vaccination rollout, but that's another story, but this is a health officer who is saying I'm going to do it to protect my father, organize a big family weekend get-together, and people are going to hug if they're vaccinated.

And again, this is the kind of messaging as clinicians that we do to recommend and to increase uptake of vaccinations. Thank you.

DR. DEL RIO: Thank you, Monica. We're going to go ahead now and talk about it. I asked the three speakers to come on and we're going to have a Q&A session.

So, I'll start with you, David. One of the questions that comes up is any thoughts on transmissibility of the New York variant, the B.1.526 variant compared to the other variants like the B.1.1.7, and why do you think it's taken over in New York?

DR. HO: Well, I don't know the reason it's taken over. It's becoming more dominant and it's outcompeting B.1.1.7 in New York City, and we know B.1.1.7 is more transmissible than the

original strain, so it's indirect evidence that this B.1.526 variant is more transmissible and that's why it's so dominant.

DR. DEL RIO: Perfect. Angie, I mean, people are asking whether there's the evolutionary tradeoff between virulence and transmissibility, such as the more transmissible variants will be less virulent. Is that the case with SARS-CoV-2?

DR. RASMUSSEN: So, I don't think we can make that assumption. I think that oftentimes that is what happens for viruses that are very lethal that typically cause very severe disease in most of the people that get them.

There is an evolutionary pressure for them to become less virulent because obviously it's not in the virus's best interest to kill its host before it can be transmitted to another host.

In the SARS-coronavirus-2, even though it spread so widely that it's still a potentially lethal virus and is a huge public health problem, it's actually not that lethal and it tends to be transmitted before people even know that they're sick.

DR. DEL RIO: Okay.

DR. RASMUSSEN: So, there's not evolutionary pressure on this virus to become further attenuated.

DR. DEL RIO: Sounds good. Monica, you talked about the variants and the vaccines, and you said it was easy to tweak them. Do you think boosters are going to be needed?

DR. GANDHI: You know, I think personally, I think it depends. You know, I think about two things when I think about boosters.

I think that one thing is that if we see the hospitalizations and deaths go down with mass rollout of vaccines, which I think the UK is again the -- well, Israel is the most dramatic example, but the UK is closest to us, at least in terms of the size of the country. Israel is quite small.

They are seeing such a massive reduction in hospitalizations and deaths. They actually had 575 people in the hospital yesterday with about 35 percent of their population vaccinated.

With that degree of defanging the virus

and making it something that isn't a concern to us as clinicians, the question will be what -- the question society, I think, will decide on is, you know, what do you impose restrictions for? We have imposed restrictions for this virus because of its severe disease.

I also think that in the future, it depends on how many people accept the vaccine now and how fast we go now, and the entire point is that if we can get --

We're going to get transmission down because I just showed you all of those real-world studies that are showing that you can't pass it on as readily if you are vaccinated. Then if you have a low level of circulating virus, then ultimately you may not need boosters for vaccines.

So, it's going to depend on our vaccine rollout, how fast we go, approving the AstraZeneca, which is, I think, going to happen in April. That's when our data is going to come. We're going to have four vaccines then.

We're going fast. We need to go faster. Everywhere needs to go faster, like the UK. We

need a national healthcare system like the UK. And I think we could get there without the need for repeat boosters.

DR. DEL RIO: Thank you.

DR. GANDHI: And we need vaccine equity as we're pushing so much for. We need global vaccine equity, and the reason that I showed those last three trials, which were AstraZeneca, Novavax, Sputnik, and also Sinovac, Sinopharm, and Covaxin, it's important to know that there are other vaccines out there that are actually much cheaper, and we need to be able to make vaccine technology globally available. We need global equity in vaccines.

DR. DEL RIO: Thank you. So, David, how about the approved monoclonal antibodies' impact on some of these variants? And there's a new monoclonal antibody also from AstraZeneca. Do you think these monoclonal antibodies will be losing effectiveness as these variants develop?

DR. HO: Yes, I think the 484K that's found in the South African variant P.1 and the New York variant has a dramatic impact on the number of antibody in use and the number in development.

The California variant with the 452R mutation also has an impact.

So, I think we -- and just this week, FDA has stipulated that Regeneron needs to track the variant viruses as they administer their antibodies. The AstraZeneca antibodies are, one of them is mildly impaired against the South African variant.

DR. DEL RIO: Thank you. Angie, there's a question here that I would like you to address which is, you know, is there pressure? Is vaccines putting pressure on the virus to mutate, especially because you're giving two doses? Will this be actually causing evolutionary pressure on the virus?

DR. RASMUSSEN: Well, it could in theory, but I don't think there's any evidence that shows that that's the case right now.

Certainly we've seen from some other work that has come out of the lab of Jesse Bloom at Fred Hutch here in Seattle that for other coronaviruses, when the population does develop immunity, that does put pressure on the virus to change antigenically, and then of course, you know,

people will be infected with the new variants. They will develop immunity to that and so on and so forth.

But right now, because vaccination has been pretty uneven around the world, and of course, different variants are circulating in different populations, I don't think that there's any evidence so far that the vaccines themselves or that prior immunity is putting a lot of evolutionary pressure on the virus.

What we are seeing is conversion evolution of mutations such as E484K. That suggests that independently numerous lineages are developing these mutations because they give an advantage to the virus in terms of transmissibility and potentially immune evasion.

But because of the E484K, one thing I didn't mention in my slides is that that mutation, in concert with the N501Y mutation, has been shown to synergistically increase binding affinity for ACE2. That suggests that there may be some other advantage besides evading the immune system that that mutation is conferring on the virus.

DR. DEL RIO: Okay, that's pretty good. Monica, this one will be for you, but everybody is welcome to also intervene.

One of the questions says if the B.1.1.7 variant would increase transmissibility is dominating in Florida and also having increased severity and mortality, then why is Florida cases and hospitalizations actually coming down?

Florida has, you know, a 14-day decline in hospitalizations. Is this because they're vaccinating more or what exactly is happening? Is this an anomaly?

DR. GANDHI: The same thing happened in Israel with 80 percent of the circulating virus being B.1.1.7 during the Pfizer rollout, and the same thing happened in the UK with probably greater than 80 percent. It started in the UK clearly.

This is happening. Vaccinations work. All of these vaccines work. Natural immunity also is obviously a true thing, and the combination of those means that we are not seeing increased cases and hospitalizations in Florida where, I think, at this point, like you said, 50 percent are B.1.1.7.

So, I think -- I keep on looking at the UK because their vaccination rate is about twice as fast as ours and things are going great.

DR. DEL RIO: Okay, David, would you recommend -- I mean, what kind of a national strategy do we need to screen for these variants in order to really pick them up and know exactly what's happening?

DR. HO: Well, I think the country is trying to increase our capacity to do genomic surveillance, and that's a good thing because we've been way behind on that.

But aside from sequencing, how we found the New York variant is to do site-specific PCR, and that could be done much faster, although you will only find what you're looking for. If there's a new variant with a new mutation, you may not find that.

So, I think we got to use all tools at our disposal to continue to do genomic surveillance at a much higher level than we have been.

DR. DEL RIO: So, you know, Angie, given that the RNA viruses mutate all of the time, how

is it possible for the vaccines, the mRNA vaccines and others, to stay ahead of the game and to be predicting what's going to happen, and what do you think companies are doing in order to modify their vaccines?

DR. RASMUSSEN: Well, I know what companies are doing to modify their vaccines is they're making boosters based on the variants that we've already discovered.

And that fortunately is very easy to do with technology like mRNA vaccines because the vaccines themselves are relatively straightforward to manufacture. It's just a matter of essentially switching out the sequence of one variant for another. I think that that answers that.

DR. DEL RIO: Okay.

DR. RASMUSSEN: I think that, you know, it's hard to predict. One of the problems that we have is that this is a completely new virus, and even though there are similarities to other betacoronaviruses, including SARS classic, it's really hard to predict what types of mutations are going to emerge.

It's really hard to predict which site is going to be important and what that mutation will be a switch to. There are, in many sites in the spike protein and elsewhere too, there is opportunities for multiple different codons to be inserted. That means different amino acids could go in that place.

There's also the opportunity for deletions, and that all can have an impact on how the spike protein is functioning, how its structure is formed. It can induce conformational changes, and all of that leads to pretty unpredictable effects.

So, it's really difficult right now to say, to look into the future in a crystal ball and say, oh, this, you know, locus is going to be mutated. I think we need to start designing a booster for that in advance. Unfortunately, a lot of this is kind of figuring it out as we go along and as we get more experimental data.

This, I think, is a very strong argument for continuing to do this type of research and making an investment in basic research when we're not having a pandemic so that we can actually get better at

predicting this sort of thing.

DR. DEL RIO: Yeah, so maybe machine learning will help us in some sort of way there?

DR. RASMUSSEN: I think machine learning does help, but that's not the only thing. I think one lesson that we should all take from this pandemic is that just throwing technology or throwing AI at a problem is not the only solution.

As somebody who uses machine learning in my own research, I obviously think that it can be beneficial, but that also needs to be -- you know, models are only as good as the data that you put into them, and that means that we need to be generating more experimental evidence as well.

DR. DEL RIO: So, one question, Monica, that people are having is, you know, how are you able -- how will we be able to sort out increases in cases due to variants versus due to behavior, you know, pandemic fatigue, increased travel, restaurant openings?

DR. GANDHI: Well, I think that is actually a really great question, and what I've been looking at, which is actually taking quite

a bit of math, is looking at the hospitalizations per case because I'm really interested, again, are we seeing decreasing severity of disease?

So, I did this this morning in New York because I was looking at the plateauing cases and someone I have now, this is automated for me every morning, is we're looking at hospitalizations per case, and again, we're seeing that as a decreasing proportion, which is really great.

That's exactly what these vaccines, I think, are doing for us. I think that's what we saw in Scotland, we're seeing in England, we're seeing in Israel. We're seeing that. I mean, I showed you that massive decrease in hospitalizations with vaccination.

So, I'm really hopeful about us remembering the T cell response when we talk about response to viruses and I'm feeling good about the T cell response being preserved across variants, the paper that I showed you, and so I'm looking at the severity of disease.

So, you're right that what could be happening is we're opening and we're also

vaccinating, and certainly public health recommendations right now nationally are not to open too fast and to be slower about things, and to have our mask mandates on and to distance, and some states are doing that and then some states are opening more quickly without the masks.

To give credit, Texas, Mississippi, Florida, places that are opening more quickly are not actually seeing increased cases to be, you know, to be very fair in terms of this question that you just raised, is it restrictions versus variants? Then again, Florida has 50 percent of the B.1.1.7 variant, so I think it's very hard to sort out right now.

I, as a public health person in San Francisco, would say let's keep our masks on. Let's keep our kind of cautious openings. We're opening more cautiously as we're applying the vaccines.

DR. DEL RIO: So, I think we're getting close to the end, so I would like to just summarize a few things that have been said today.

I think number one is that RNA viruses mutate. Mutations will continue to happen, and

this is part of the natural lifecycle of this virus and we need to be aware of them.

We also need to be looking for them and doing sequencing and doing other strategies to look at these variants. I think it's going to be important and something we need to continue to do, and then continue to study how the different antibodies improved by the vaccines are actually, you know, inhibiting or not inhibiting these variants.

I think so far, the evidence suggests that the vaccines are effective against severe disease and hospitalizations. There is some concern about some of the vaccines not being as effective against some of the variants, and one of them, for example, the B.1.351 variant from South Africa, and some of the other variants we'll have to see over time.

But I think the data on the vaccines overall seems to be very encouraging. They seem to be able to also probably prevent infection, and they may very well be able to halt transmission.

So, I think at the end of the day, the conversation needs to be continue vaccinating.

Continue monitoring for variants, and in this race between variants and vaccines, we hope that vaccines will win.

But we have to be aware that as long as there's COVID around the world, there will be variants emerging in different places around the world, and we're not safe until everybody is safe, so we need to be sure that vaccination gets to every corner of the world if we are to prevent indeed these variants.

So, I want to at this point in time thank our participants for an excellent webinar and excellent presentations. This concludes the webinar. If you were registered for today's webinar, you will receive an invitation to the next webinar.

This webinar has been recorded, and the recording, and transcripts, and the slide presentations will be available at the covid19converations.org website. Please also note upcoming events there and also about past webinars that you can watch.

There is a Climate Conversation webinar

coming up, the upcoming event on March 18 at 3:00 p.m. that I would encourage you to look at. Climate and COVID are two very related issues and two major health problems right now globally.

And I want to thank everybody on behalf of the panelists, on behalf of the American Public Health Association and the National Academy of Medicine who have sponsored this webinar, and with this, we will complete today's presentation. Thanks, everybody.

(Whereupon, the above-entitled matter went off the record at 6:28 p.m.)