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SARS-CoV-2 Variants

Announcer:
Welcome to CME on ReachMD. This CME activity titled: SARS-CoV2 Variants is brought to you by AKH Incorporated, Advancing Knowledge in Healthcare, and American Thoracic Society, and supported by an educational grant from GlaxoSmithKline. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Auwaerter:
Hello, and welcome to Rapidly Changing COVID-19, The role of Monoclonal Antibodies. I'm delighted you could join this program. I'm Dr. Paul Auwaerter. I'm the Clinical Director for the Division of Infectious Diseases and the Sherrilyn and Ken Fisher Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore.

This CME program will focus upon a SARS-CoV-2 variants, and there are two other segments that you can also see, but the learning objectives in this segment will identify the variants that are currently causing issues that result in hospitalization, severe disease such as ARDS, and then differentiate the variants with regards to morbidity, mortality susceptibility, and also especially in another segment, potential treatments that will be important for some of our patients.

Now, here's the agenda we'll be focusing on over the next few minutes of this hour. And that's an introduction and overview of the Coronavirus. Focus then on the current variants along with transmissibility, and how our current vaccines and monoclonal antibody treatments are effective, along with summary and conclusions, of course, then the post-test, as well as question and answer period.

So, regarding virology of SARS-CoV-2, the focus for this, of course, rapidly became those patients ill enough to require hospitalization. That's how this was first identified in China, and also the cases we intended to focus on early in the pandemic in 2020, when it arrived here in North America.

Unfortunately, through a variety of reasons, including just the extraordinary transmissibility of this virus, as of early July of 2022, over a half a billion people have been infected worldwide with the virus, including nearly 90 million in the United States. There have been over 6 million deaths worldwide and over a million deaths in the United States. But I have to say, there's data suggesting that the attributable mortality, total people that have died might be well over 3 million people. If you actually look at mortality within the United States, that's much higher over baseline over the past 2 years.

Transmission, I'm sure as many of you know, is respiratory, both droplet and we've come to know aerosolization.

And in terms of immune responses, we do know that neutralizing antibodies can be quite protective if they're very well matched in terms of targeting the existing variants. And cell-mediated immune responsive and so-called adaptive immunity with both cell-mediated and CD8 responses specifically, are important for clearing the virus, but are also those that tend to be triggered a few days into the infection as opposed to early innate immunity.

The virus itself is an RNA virus that has components of structural proteins that you see identified here. We'll be focusing on the trimetric spike protein, which has co-opted a normal protein on cells ACE-2 receptor, which is well presented, especially in certain organs, such as the heart and lungs. And this protein will bind and then provide a fusion into the membrane entering the host cell The receptor-

binding domain is the sort of critical part, and probably the most conserved part of the spike protein. Although as you'll see, there are a number of changes in this particular protein structure that have caused issues as time has gone along.

So this critical spike protein with its trimetric structure is the operative end of where neutralizing antibodies work. And antibodies that neutralize help prevent productive infection of cells or bind to virus that, therefore, will render it unable to participate at that stage.

Now, this trimeric protein has sort of an up and down structure, open and closed. The idea is that when the virus is more exposed and open, there's greater potential for different antibodies to bind to the spike protein. When it's more in that closed or down perspective, it doesn't end. As this virus has acquired mutations, and again, the mutations are a natural consequences, especially of RNA viruses that don't have the greatest fidelity of its RNA polymerase, most of those mutations render nonproductive virus in aspects. But occasionally there are those that enhance the efficiency of the virus and evade immunity. And what's happened is those mutations, especially in the spike protein, have caused the virus to develop spike proteins that are a little more in the down or closed position. But they also have facilitated greater binding to the ACE-2 receptor, which is probably one of the reasons it has increased its transmissibility greatly.

So monoclonal antibodies, or antibodies for vaccines that provide neutralization or perhaps monoclonal antibody treatments, all may behave the same way. And the neutralization destroys the appropriate pre-fusion spike confirmations necessary for adequate binding. So it's really a steric hindrance issue. But hopefully, there's sufficient antibodies. And this is one of the reasons boosters have been important as an effort to try to increase the numbers of antibodies because, especially when viruses present very large numbers, it's helpful to have vigorous amounts of neutralizing antibodies present to really do the best job in preventing productive infection of cells.

Now, mutations, as we've already discussed, of course, affect the genomic RNA of the virus. And within the cytoplasm of the virus, RNA will be transcribed. And indeed, there's a double-strand intermediary that helps trigger a danger signal in the host immune response there, but as it's being made into a new single-strand RNA to make new virus, these copying errors, just introduced by normal frequencies, mutations, and therefore some of these are the ones that have been contributing.

Now, how these develop. One hypothesis is people with chronic infections, because their immune deficient, have more opportunities for this kind of situation to occur. But honestly, one of the reasons that pandemic has not been declared ended is the huge number of ongoing infections without respect to seasonality. And just because we have millions of infections on any given day, many of them now no longer are reported, the chances of these mutations occurring are very high. So I think we'll see continued evolution of the Coronavirus that is important. And we'll get to some of those definitions as to why variants that continue to form - develop and then become prominent, meaning that it's very hard to end the pandemic until the total number of worldwide infections is significantly reduced.

Now, the ancestral strain of which the vaccine is based, was the so-called strain that ___presence of it, position 614 in the spike protein. And within short order, if you think if the COVID illness was discovered in December, but the virus isolate in January, and maybe this illness existed for two or three months, perhaps a little bit longer, of course, this is all conjecture, G4 -614 was identified – and it's not - just so it's clear, in February of 20, that's not February of 22, but February of 20 - became identified then became predominant by the spring worldwide. And this polymorphism change led to higher viral carriage in the respiratory tract and also enhanced the binding to the ACE-2 receptor, which is a common theme with each progressive mutation. And therefore, you had more transmission compared to the ancestral strain.

So as we head into variants of concern, interestingly, these have been occurring in faster and faster transitions, compared to earlier in the pandemic. And the designation was developed by the WHO, and we'll get to the definitions later on. But importantly, both the WHO and the United States Centers for Disease Control will outline what they view as current variants of concern, and also at least genomic search surveillance, to try to keep a handle on what's happening in communities across the United States. But also, other countries have really been at the forefront of this such as United Kingdom and others.

So our current Omicron variant, which was identified in November of 2021 in South Africa, was really interesting, because it had over 30 new mutations in spike protein. This was not just some evolution from the prior predominant variant of concern, Delta, this was a wholesale shift. And we'll see why in a moment. But as of early July of this year, that's 2022, these Omicron subvariants are now really 100% responsible for COVID variants in the United States. And we see no evidence of Delta, Alpha or some of the earlier variants that concern that had been sort of troublesome and causing vast amounts of patient illness, hospitalizations, and deaths.

So Omicron has even higher replication rate than earlier variants such as Delta, and with clearly higher household attack rates that have been outlined in a variety of countries, but perhaps first reported by the United Kingdom. Where in Europe, we tend to inherit the variants that seemed to occur in Europe, 4 to 8 weeks afterwards. And that certainly been the pace throughout this pandemic. And another study from the U.S. suggested the secondary attack rates have climbed to as high as 53%. Of course, this is in a setting where there's a fair amount of pre-existing immunity and immunizations.

So this is the latest snapshot as of July 2, 2022, of the genomic surveillance. But the caveats now exist that with home antigen testing, many infections are not being reported or people are not even seeking a diagnosis, especially for mild disease. So I'm not sure we have a complete picture. But what these colors tell us are the darker purples representing the earliest Omicron variant, subvariants, have nearly vanished by May. And then we were dealing with BA.2.12.1. But now, the green bar, that's representing BA5 and BA.4, which are very closely related, now account for the predominant variants that have been sequenced at all the sentinel sites that the CDC works with, which are a number of academic medical centers and state labs. But you can see this has been occurring in just a matter of weeks. And this is very fast moving.

What we know from observational data, though, is that although there's increased transmissibility, which is why we're seeing these changes in the subvariants occur faster and faster. Despite this increased transmissibility and attack rates, the risk of severe disease seems to be lower. So we have fewer people in the hospital, and certainly fewer deaths, with now averaging about 400 deaths a day being reported in the United States, as opposed to the thousands that we saw in their earliest phases of Omicron. And this may reflect truly, that so many people got Omicron earlier this winter, that they have some immunity, whether they've been - even if they were not immunized.

But the other thing that's important to know is that if you had Omicron, in December and January with BA.1 and something along those lines, that you're not getting great protective immunity against 4 and 5. And we've seen people in as little as 30 or 45 days after getting documented Omicron - after getting documented early Omicron infection, get a subvariant, such as BA.4 or 5, that has been proven by differences in sequencing. So protective immunity from any infection has sort of been declining as this virus gains traction and additional mutations to evade existing immunity.

So the decreased severity certainly has been first reported in South Africa where of course the Omicron wave first occurred. And you can see compared to Delta and earlier variants that the amount of people landing in the ICU or dying is markedly less, still above what we would see with seasonal influenza, which I think is very important to put into some context. But I'm certain all of you who are critical care physicians and working in ICUs or intermediate-level units, have certainly seen fewer numbers as we move to spring and summer here in North America.

As I've hinted at earlier, protection against Omicron if you've had prior SARS-CoV-2 infection has been less. And this is as viruses evolve, especially with changes in the spike protein that has allowed it to evade pre-existing immunity. Now, the pre-existing immunity, I think still gives you, or affords you I should say, protection against severe disease and death. Of course, it's not universal in that regard. And certainly, if people have immune deficiencies of some nature, or are taking medications that prevent full immune responses, then that degree of protection from severe illness is less. But this is still quite important, why we're still recommending vaccines and boosters in people, especially as time goes on, as the immunity to the Coronavirus does indeed wane. But importantly, if you have had COVID in the past and relying on that to help you evade new infections, then you can count on that less and less over time.

Now for the Omicron variant. You know, we've discussed the vaccine issues here. Specifically, if we look at the Pfizer vaccine against Omicron in South America - I'm sorry South Africa, the Delta surge where it's still behaved very well there in terms of vaccine efficacy, that's preventing both infection, but here just protecting against hospitalization, certainly was less. Still substantial against the Omicron variant but definitely less than was seen with Delta. And this no doubt reflects some of those evolutionary changes in the spike protein. Now, this is, again, just with the Pfizer vaccine, which was used in South Africa, should know that a large number of people also got the Janssen vaccine in South Africa, but this is just reflecting of those that got the mRNA vaccine.

And then, from some U.S. data, you can see that, at least here in North America, and again, our populations are different, if you look at hospitalization protection, it looks better than we see in South Africa. And it may be because people have gotten an initial - a third booster here, much more commonly than we that - than was done in South Africa. And still seeking, you know, medical visits perhaps a little more frequently, but still is holding up quite well. And I've always told patients that being fully up to date, which is the CDC parlance, that getting two boosters, if you qualify if you're over the age of 50, is what I urge, it's what I've done.

I had COVID-19, myself the same day as Tony Fauci acquired it. I had a second booster, I'm 60, have some other health problems, but didn't land in the hospital at all, and just felt like I had a moderate flu-like syndrome, certainly knocked out for a couple of days from going to work, but nothing severe.

So I do encourage people to get those additional boosters because it does appear to correlate with preventing that severe illness that has really caused so much illness and death, with hospitalizations in that second week of infection.

Now we're dealing with sub-lineages, we – after BA.1, we saw a large amount of BA.2, that was the orange bars in that U.S. genomic surveillance, still circulating to a degree here in early July. This had even more mutations and really differed from BA.1. BA.1 differs quite a bit from the BA.2 variants, and BA.2 has led to 4 and 5, which we'll discuss shortly. And there is certainly a difference between

the two. But interestingly, the mutations in BA.2 seem that it's even more transmissible than BA.1. But there does not appear to be marked differences in virulence, or so-called pathogenicity. And it looks like the vaccine responses that we're currently using appear to be relatively equivalent. But reinfections can occur. So BA.2 was different enough that even people that had earlier Omicron infection, as we've mentioned, have been infected in short order again. But certainly, unimmunized people are those most susceptible.

This gives you an idea where certainly in the first part of the Omicron era, we had BA.1, 2, and 3, we now have 4 and 5, but if you look at those, there's a fair amount of overlap. But it does give you a flavor that each of these and the reason these sub-lineages are identified separately, is there is some significant mutational differences amongst each of these on the Venn diagram.

This is from a website that I look at frequently provided by the NIH that catalogs available studies, in vitro studies that look at neutralizing activity of monoclonals. The site also has sera from clinical trials and vaccine-induced immunity as well as antivirals. But importantly, if we're just looking at antibody-based treatments, unfortunately, we only have two currently in use under FDA emergency use authorization. And what you can see here with the dark grey dots are that if you look at the monoclonal bebtelovimab, the bottom green arrow pointing there, it compared to reference strains, had very little change in neutralizing activities, still quite active against BA.4 and BA5, which is what all these dark grey dots represent.

However, if you look to the top green arrow Evusheld, the trade name that's the combination that you see below under the yellow highlight, the cilgavimab and tixagevimab, does have maybe a 10 to 30-ish-fold reduction in neutralizing activity. And that's perhaps based on the fact that tixagevimab really has little apparent activity against 4 and 5, so you're really left with the cilgavimab.

So whether this is sufficient to prevent breakthrough infections in those immunodeficient patients that have received the monoclonal antibody combination for pre-exposure prophylaxis, I think we will soon learn, certainly those are breakthroughs even earlier, when it had good activity against earlier variant – Omicron variants. However, it's still under use at the moment, and we don't really have any other products available at the moment. As you can see here amongst all of the monoclonal antibodies, there really isn't any that have the activity of bebtelovimab.

So the Omicron sub-lineage BA.2 really rendered preexisting monoclonals that had been used quite regularly, which included sotrovimab, no longer effective, and when Omicron hit in December, we knew that casirivimab, imdevimab, bamlanivimab, and etesevimab really did not have a sufficient activity. So those EUAs ways were revoked.

Now, I'd like to just go back a little bit to the summer of 2021 when the Delta variant, which first was identified in India, became prevalent quickly in the United States through the summer and fall of 2021. And that virus, which really wreaked havoc, not only here in the U.S., but in many other countries, including India, which has largely escaped significant impact of the pandemic to that point, has a many more mutations in Omicron. And I think you get the sense of the changes in this trimeric spike protein, that's substantially more. Now, as the note says here, it doesn't mean that overcrowding is more dangerous, but it did lead to increased transmissibility as we've discussed.

If we look at R-naught, and this is a so-called replicate - reproduction number, that is the number of, if you have an infected individual, how many people might they go on to infect if they're not isolating and so on. And you have a number of factors here, which are estimates. And you can see, if you look at the bottom, the ancestral strain had an R-naught, that was perhaps 2 to 4, so maybe 3, 2.5. Alpha had a higher R-naught, Delta, and then you have BA.2. Not reflected on this graph is data from South Africa, where estimates for BA.4 and BA5, the current predominant subvariants in the United States, had an R-naught of 18.6, which places it squarely as infectious as measles, which is really one of the most contagious viruses that we've known for years, which is why we've been so concerned about maintaining vaccine-induced immunity to prevent outbreaks in United States, such as the large one that occurred in Disneyland in California in 2014. So this certainly is worrisome. And I think one of the reasons why many of you have had family, friends, perhaps yourself who have escaped COVID-19 for over 2 years now with this illness, despite immunization.

Part of the reason it's hard to anticipate what might happen down the road if future casting for what will happen in a pandemic is so fraught with issues, is that there's no natural evolution of these pathogens. And as you can see, you know, it's not as though Alpha lead to Delta. In fact, they're widely separate. It's not as though Delta lead to Omicron, for example. Now, what you have seen is that the subvariants from Omicron originally identified, have had some evolution. So you see, that led to BA.2, and then to 4 or 5, as well as 2.12.1. These last three are the ones that are now circulating in the U.S. And this is because there's really not enough distinguishing features in these latest to be called a separate variant of concern, but rather subvariants.

Now, the WHO has developed a variety of designations in the past - I'm sorry, at the start of the pandemic, to try to keep track of these variants. And I'm not going to go through all of their categories. But variants being monitored is something that you might see when you look at the WHO site, or others. And this just means that there are variants that appear to have been then described by the genomic surveillance, they might have some mutations that make virologists concern, but we've seen similar variants that are being monitored,

never really pan out. Some people have even called them scariants, because early on, and a lot of the newspapers focused on these and so on, but they never really quite amounted to anything. So this is something I think more for public health officials, virologists, and infectious disease people to look at, but is a category that is being monitored under the pandemic.

It's the variants of concern that really have caused the health problems in the pandemic largely. And the WHO has this working definition. And this means that there's some increase in transmissibility or detrimental change in the way the infection has spread, or increased virulence or change in disease presentation, or that social measures and mitigation measures or vaccines or therapeutics have a marked decrease in their effectiveness.

At the moment, there's only one variant of concern, that's Omicron, and we'll deal with in a moment about so-called subvariants. But this was first identified in November. And you see some of the key mutations that are being monitored that have accounted for this as being a separate variant of concern compared to earlier variants.

Previous variants of concern, once the WHO adopted this set of labels, include Alpha, Beta, Gamma, which had a short run, and Epsilon. Where we are now largely is variants of concern with sub-lineages under monitoring the rather awkward VOC-LUM. And this is busy because there are a lot of them and such as BA.4 and 5 and 2.12.1, but there are four others. And these remain in this certain category, which is a new category, but are being tracked as all Omicron, unless one of these variants, or a subsequent future variant, seems to behave markedly different and would fit more the criteria outlined in the working definition for variants of concern.

Some of the points that I think are important and have been largely learned over time is that each of the subsequent variants have become more transmissible, their R-naught has increased. And this is despite a fair amount of acquired immunity, either through vaccines or infection.

However, probably the most pathogenic of the viruses was Delta. And since Delta, Omicron certainly has caused less severe disease. But as the tree showed, it's hard to predict where the next variant will come. We hope it will lessen in severity over time, but there's no guarantee, and that was the case with Delta. The BA.5, and to a lesser degree BA.4, are now the predominant variants circulating the United States, which are highly transmissible, but again, have not yet accounted for a significant increase in disease severity, but still are hospitalizing more people, resulting in more deaths than we have seen with seasonal influenza. In fact, for what it's worth, projections presented recently to the FDA have suggested that anywhere from 95,000 to 211,000 deaths may occur due to these variants and whatever future variants will hold between March of 2022 and March of 2023. So over 1 year, still far more deaths than might be anticipated from seasonal influenza. And that's anticipating that we may have a novel variant come this respiratory season in the fall.

And there is little doubt in my mind, given the extensive number of infections still occurring by the millions, that variants will continue to evolve and work to evade existing immunity and also monoclonal antibody treatments. I hope this isn't the case, but means that the importance of supportive care if people do land in the ICU, and also engagement of antiviral strategies that are more directly acting, such as remdesivir or earlier treatment with nirmatrelvir and ritonavir will be important.

I truly thank you for listening to this program. We will now follow with a post-test and requirements for getting your CME certifications. I thank you so much for listening. And please tune in to the other two components of this webinar series.

Announcer:
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