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SEXUAL HEALTH ECHO: COVID VACCINES: UPDATES AND CHALLENGES

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Sexual Health ECHO: COVID Vaccines: Updates and Challenges
[video transcript]

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Over to Dr. Branche who will be giving us an update on COVID vaccines.

0:18
Okay, great. So um, I'll just preface this by saying that, you know, I'm sort of a vaccine ologists and a respiratory biologist. So a lot of what I'll be sharing will be more about the science behind where we go now in terms of COVID vaccines, and less about things like efficacy and side effects. I mean, we could certainly talk about those things, but it keeping up with the variance and how the pandemic is unfolding, has become largely about understanding the science of the immune system. And so that's where a lot of efforts are being focused. And I'd like to just share a little bit about that

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with you today. So I don't have anything to disclose. And then this talk is called COVID-19, vaccines, updates and challenges.

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There are two there'll be two learning objectives to review the science surrounding development as well as what we call the current antigenic landscape. And I'll talk a little bit about that. And then you know, how vaccine has policy updates have sort of evolved and how to apply them to our patient population. So this talk used to actually be called COVID-19 vaccines staying ahead of the variance. Is that possible? And then I realized I couldn't answer that question. And it just kind of made us all very fearful. So this is the new way I'm sort of talking about this. So as as many of you are aware, we started working on developing COVID-19 vaccines mid 2020. By the end of 2020, we had amazingly effective vaccines that we were able to start to deploy at the end of 2020, and 2021. Because the majority of people in the world had no immunity against the source transfer virus, giving the COVID-19 vaccines primary series which were given primarily as two dose vaccines for the Johnson and Johnson vaccine is the single dose that was actually able to rapidly establish immunity. And you could measure immunity by looking at things like antibody levels, as well as how your T cells and B cells were producing other types of immunity. So after we gave that primary series vaccine, we saw this rapid increase in immunity, especially people who've never been infected. And you can actually correlate that immunity to protection against not just severe disease and hospitalization but infection in general, which is pretty remarkable. As you know, the flu vaccines don't always prevent people from becoming infected with the flu. But it usually almost always prevents you

from getting very, very sick. And so we didn't know what we were going to be able to accomplish with the COVID vaccines since the find out that they not only prevented people from being hospitalized, but that they in 90%, or better of cases in that first year prevented even infection was just a remarkable outcome. What we saw was that, over time, as we expected, antibody levels don't stay static. They do decrease over time. And what you have after that is memory immunity. And so we started to see within six months of people having received their primary series that their antibody levels waned, and that the weighting of those antibody levels did correlate with the ability to develop breakthrough infections. So antibody levels go down, breakthrough infections go up. And that was really the rationale for starting to boost people towards the end of 2021. And so we started to boost everyone if you were at least six months out from your primary series. And that restored a lot of the immunity that we saw with the primary series is this is 2021. So we were really seeing infections with alpha with Delta, and alpha and delta variants, those viruses are so similar to the ancestral virus or the original virus, that this restoration of infection of immunity not just prevented people from becoming sick, but it also to some extent, we stored protection against even becoming infected and we were seeing efficacy levels against alpha and delta, as high as seven days and 80% which was which was great. So we had about a year maybe a year and three months or so of having sort of a strategy that they knew would protect the vast majority people from becoming infected and ending up with a more severe illness. And then we started to see other variants emerge things like data. And then of course, the Omicron be a one wave at the beginning of last year. And when we started to look at how, what these antibodies are getting from both the primary series, and in the primary series and booths performed against various different variants, what we saw was that it wasn't equal and so appear in black is the earlier strain the ancestral strain. And then these are various different variants. And when you get down to beta here, which, at the time this study was done was the most different variants from the obsessional string, you can see that a month after vaccination, and then when you look out, you know, at six months at eight months, that the levels of antibodies, so it's just what you're measuring here on the y axis are just a lot lower to begin with. And not only are they lower than what you see against the original strains, they also seem to decline a little bit quicker. So that was our first clue, sort of mid 20, mid to late 2021, that as the virus continued to change, and to evolve, that there was going to be some degree of immune escape, these antibodies weren't going to do what we needed them to do, like for in every case, in terms of preventing infection. And perhaps they wouldn't do what the most important thing was just preventing people from being hospitalized. And so that's when sort of the idea behind updating the vaccines sort of came into play. This is another study that we were doing simultaneously at the NIH was funding that we also were able to participate within here at U of R, where we boosted people with different sort of combinations of things. And so this is the study that really established the safety and the ability of being able to mix and match vaccines that you didn't have to keep getting Pfizer if Pfizer is what you got originally. And so that was a really pivotal study, that

helped us define vaccine policy and 2021 and 2022. But we also were able to look at responses against Omicron when Omar Khan emerged, sort of in the beginning of 2022. And what we were seeing was that similar to what we saw with beta, where the blue lines are sort of the antibody titers, you're getting against the ancestral strain, and the yellow lines are all a con being one that you started off much slower even after you were boosted here. But then you also have the slope that's a little bit more sharp, suggesting that even from 30 to 90 days after your boost, you're seeing sort of a more rapid decay in antibody levels, which means as those antibody gloves go down much quicker, that interval that you're protected, potentially become shorter. And so that was more justification, again, that Omicron similar to beta was going to potentially result in less protection even in fully vaccinated and boosted individuals. So that's really all we had, at the time that the FDA, and the European agency that's similar to the FDA really decided that we needed to make a recommendation, even though we didn't have all the data that we needed, on how and when to update vaccines. And so, the inherent United States, the FDA vaccine committee met in June of 2022. They saw the totality of the data that we had, they realized that giving it more doses of the original vaccine wasn't going to get the job done. Because the antibodies were lower, they were disappearing more rapidly. And therefore you could infer that protection wouldn't be as great. And so they made the recommendation to update the vaccine. Now at the time in June, when they made that recommendation, we were still seeing primarily Omicron BA one causing infections in the United States and around the world. But we'd also start to see the emergence of the BA four and BA five some variants, we usually link those two together because they're so similar. And so here in the United States, the FDA said Well, let's go where the vet virus is going. We know BA four and five is probably going to be the next wave this this later this summer in the fall. Let's update the vaccine to a hybrid vaccine that's half, original and half BA four five And Europe went in a slightly different direction. They said, Let's update the vaccine with Omicron being one, which is the original Omicron, and then half the original vaccine. And so in Europe and most of the world, they're using a by Valent vaccine, that's the prototype or the original plus being one. And here in the United States, we're really the only people that are using all Muckrock plus be a four five by availing vaccine. And, you know, for better or worse, that probably was a good decision, because we then had this huge be a four or five wave here in the United States, around August and into September, and October, and then be a four, five start go away. Now we're dealing with SPD one and 1.1, and all these new other variants that, you know, it's not even important to remember their names because they come and they go so quickly.

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So here in the United States, you know, we updated those vaccines, we vaccinated people, unfortunately, only about 20 to 30% of people who could have gotten an updated booster actually went out and got one. And even with that, we're still not seeing the efficacy that we saw against original strains of the vaccine. This is some data that was compiled by the CDC,

increasing community access to SARS COV testing program, where they looked at efficacy during the BA four, five way from September 14 to November. And they basically compared the effectiveness of getting the buy Valent boosts compared to not getting the Bible boost and just having gotten the primary series and then the original boost. And what they saw was if you compare the efficacy or effectiveness against people who did and didn't get that by availing boosts, you are seeing a benefit with the by Valent boosts, especially in younger people, the difference in effectiveness was 30% versus 56%. As well as in older adults as and again, the difference in effectiveness was 31 to 48%, in middle aged adults and 28 to 43%. So clear benefit of the buy Valent boost. And this is just looking at symptomatic COVID. This isn't even looking at how well the buy valium was prevented hospitalizations. And so this is some of the earliest real world effectiveness data. And really, like maybe the only thing that actually shows what we suspect to be true, which is that the vaccines didn't need to be updated, and updating the vaccines would correlate with better protection overall. But as I said, That's old news. Because that was during the BA four when b four five was circulating. So here's b a five wave, the BA five wave sort of started predominating towards the end of August and persisted as the dominant strain here in the United States through October. And since the beginning of November, we started to see other strains emerge. B, q1 b q 1.1. And if you following the news, this is even old news itself, because now we have x DB one, which I was fortunate to be infected with last week, so not pleasant. So we know that the virus will continue to emerge. And it's almost impossible to predict what it's going to do next. There's two ways that the virus can continue to evolve. What is what happened when it moved from delta to Oh makan, which is that if you think of this as sort of a tree, and each branch is like an entirely new kind of strain, when it's switched from delta to Omicron, that developed an entirely new branch on the tree. And so those deltas on ICANN are actually very, very different from each other, and which is why we needed to update the vaccines. Or it's possible that the new variants will just continue to sort of branch off of the Omicron branch, which is what typically happens with most seasonal Coronavirus and many influenza viruses. So we don't actually yet know enough to be able to say which one of those these two things are going to happen. Although our experience of the last year suggests that there's something about the Omicron branch of viruses that makes it more fit. And for that reason, it seems to continue to just be evolving from this law. Aren't your branch here. So it's possible that that may be how SARS COV two virus evolves over time. And that'll make it easier for us to actually develop vaccines, and to update vaccines that if it were to develop an entirely new branch with an entirely new strain that we couldn't predict. So that's how we're thinking about it going forward. But I think we also have to think about what we want to accomplish with these vaccines, you know, with a primary regimen, when at the height of the pandemic, when no one really had immunity, we really wanted to prevent any infection as much infection as possible, because preventing infection would also prevent transmission, which would keep people safer. And so early on, and I liked this, this figure from Dan Baruch it published a couple of months ago, because it just really sort of highlights how we're shifting the

science and thinking about what we want to do with these vaccines. So early on, primary infections were prevented by having really high level of antibodies, and your cellular immunity or T cells didn't really matter at all. But when you start thinking about severe disease and hospitalization, while antibodies do a really good job of neutralizing the virus, preventing infection helping you to clear the virus, once you do become infected, it's really your cellular immunity that's going to prevent sort of more severe outcomes, severe disease and hospitalizations, and even death. And so, you know, while we would love to continue to vaccinate people, and know that they'll have really super high antibody levels against all the variants that come out and prevent infection, what we really want to explore and want to make sure that we're doing is accomplishing this. So thinking more along on this spectrum, given that everybody now has some immunity either from vaccination from infection, or both. do how do we can we sort of continue to improve upon the cellular immunity that vaccines confer so that, you know, you might get a bad cold or a mild cold, but you're not going to get hospitalized from COVID? So there's several ways that you can kind of approach further vaccine development to maintain immunity to SARS Coronavirus to the first thing could be at this point, maybe we stopped boosting entirely. Everybody has memory immunity now. And your memory immunity will continue to itself refine over time. And so it's possible that if SARS Coronavirus, two becomes like other seasonal Corona viruses that we get infected with, you know, dozens of times throughout our lifetime, then you can just rely on the existing memory you have to continue to protect you. The problem with that strategy is that we know that giving boosters does in fact, improve your memory immunity. So this is again from the mix and match study where we gave that third dose or sometimes second dose, but again, that first booster using a variety of different mixings of vaccine types and platforms. And what we found is that with the exception of the Johnson and Johnson vaccine, if you boosted someone with an mRNA vaccine, you did improve their T cell responses after that boosts. And so there's room to grow in terms of the cellular immunity. The reason why we didn't see it with the people who got two doses of Johnson and Johnson is because Johnson and Johnson have these three vaccines or four vaccines that are available in the United States actually gives you sort of the most robust and long lasting cellular immunity. And so, you know, we've always thought that there was sort of a an advantage to the Johnson and Johnson vaccine platform. It's unfortunate that it had some side effects that makes it much less used here in the United States. But you know, one of the benefits of it is that cellular immunity component. So you know, there's room to grow in the immune response. So stop boosting is probably not a strategy we're going to employ anytime soon. And another possibility would just to give additional doses of whatever is currently approved. And so maybe we give another dose of the Bible of vaccine next year. But you know, we're already moving away from the idea that which is why we updated the vaccine to the first in the first place. And that's because we know that when you match the vaccine strain to whatever circulating you'll get the best immune response. Whereas if you give a vaccine with a strain that is very, very different than what are killing. So if I gave you the original vaccine, and I

tried to give you immunity against Omicron, VA four or five, you wouldn't get as good immunity as if I gave you a BA for five vaccine. And that's something else that we learned from this mix and match study. So it's probably not anything that we're going to, we're not going to have the same vaccine every year. For anytime in the near future, I suspect we will continue to update vaccines on a yearly basis, at least for the next three to five years, until you know, the rate at which the virus and new variants emerge, and the evolution of the virus sort of slows down a bit.

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So, you know, that leaves us with continue to update vaccines. And the challenge with that, of course, is that you need to be able to update the vaccine to go where the virus is going. But since we can never predict where the virus is going yet, I mean, I don't know, maybe some new suddenly, some new science will come out that improves that. But I'm not a good enough neurologist to be able to say how and when and if that's possible. So for now, it's almost impossible to have the vaccine keep up with a variant. And so we're sort of stuck with what we do with flu, which is coming up with a combination that will give you the broadest possible protection against as many variants as possible. So there's a study, I'd like to talk to tell you a little bit about that, that that that we're using NIH is using to sort of develop the science that's going to help us know what to do this fall and next fall and in the foreseeable future. It's called a Cobell trial. And it's really again, looking at various different bi veilige, or multi valen combinations of vaccines to see how do you optimize immune coverage for not just what's circulating now, but new variants as they emerge, it's really designed to look beyond what's currently circulating. And so it's a study where we, you know, we've used lots of different vaccine types, we've been using the Moderna, the Pfizer vaccine, we've been using Sanofi, which is a protein vaccine that was recently approved. And we basically make multiple different combinations of vaccines, like a vaccine with a beta and Omicron strain, or a vaccine with just the beta strain, or an Omicron plus the original vaccine, or delta plus the original vaccine. And then we see how the well that covers sort of the known antigenic space. So this is sort of some of the data and how it looks, when we develop these studies, you're able to sort of look at antibody titers against different variants. So each one of these graphs, looks at antibody titers against a variant. So this will be the original strain, this would be a beta strain as being one and this is B four, five, each line represents one of these vaccine combinations. And then all, each time point is sort of a time point after vaccination. And so you can look at it this way. And you can see do one of these arms sort of looked better than the other. And just looking at an eyeball test, you can see the red arm is lower in most of these graphs than all the others, and the red arm is actually the original vaccine. So one of the things we're learning is that if you give almost anything except the original vaccine, you'll get better antibody titers against some of these variants. And so what we don't want to keep doing is giving people the original vaccine. And so I don't think any future generations of vaccines will contain that original strain. It's just

sort of not ideal anymore. And then we can sort of, you know, look at the absolute titers and how they compare to sort of the antibody titers and how those titers compared to the titers we were getting against the original viruses. And as you can see, when you look at antibody titers measured here on the y axis, and you compare those titers with the by Valent vaccine to the titers, you might have flattened against the original strain, you can see there's about a 13 fold difference. And so even if you give an Omicron by Valent vaccine, you're not getting the very, very high antibody titers that we saw originally 2021 But you probably don't need those anymore. Both because you'd have cellular immunity and because you never needed, you know, 100,000 antibodies to protect you against infection you probably only ever needed about 1000 And so we're seeing probably sick Should antibodies with a five gallon boost to protect people, even though it's not as high as we are seeing originally. I'm just gonna skip ahead a little bit for the purposes of time. This is another way we kind of think about these vaccines. And so each one of these lines sort of represents a vaccine combination. And then you can sort of look at how well this vaccine compares to prototype and prototypes the original vaccine against the four, five, and it kind of gives you a ratio. So for example, the overcome VA one and prototype by Valent vaccine that they're using in Europe is about two times better than the original vaccine. And so looking at this sort of ratios, how helps us to, if given one of these combinations will sort of give you better protection and better immunity against whatever it is you're trying to protect. And that's sort of what they've been doing with the pharmaceutical companies. So this is data from Omicron . Looking at the same thing, this is the ratio of how the buy Valent vaccine compares to the original vaccine, just like I showed you against BA one. And so this is what the this is the kind of data that the pharmaceutical companies, both Moderna and Pfizer come up with that they present to the FDA, which is then what they use to approve or not approve a vaccine, and they'll generate similar data for whatever they updated with this year. And then the last thing I wanted to show you is that there is a huge, huge difference in the type of immunity that these vaccines produce and people who have and have never had an infection. So this is the Moderna arms of our study. All six arms, different vaccine combinations. This is the antibody titers that you're seeing to Omicron VA four, five, this baffles people who have never had an infection. This is graphic people who have had an infection. And as you can see, the peak here, I take 29 After a boost in uninfected people is sort of the starting point before boosts have previously infected people. And so hybrid immunity is actually probably the most important thing in terms of protecting people in the future have a hybrid immunity is sort of the best protection, you're gonna have been both boosted and vaccinated. And even if you have that hybrid immunity, though, getting a boost does improve your antibody titers, which will just give you better protection in general, which is why we're not going to rely just on the immunity you get from being infected, we're always going to say that hybrid is really the best combination. And then the last thing I wanted to show you is sort of this really neat tool, visualization tool that helps us to really think about how these variants relate to each other, and how you might develop a vaccine, that is going to give you the best protection. So this is

something called intergenic cartography. And what it does is that it sort of puts on a map on this visualization to how the variants relate to one another in terms of immunity. And each and the distance sort of represents how different that new variant is from the starting point, which is the ancestral virus, the original virus. And so if you think about sort of, have this is like a map, where you're getting distance, you really want to give a vaccine, which ideally will cover the entire map. And so if you gave a vaccine, for example, that has beta plus the original strain, you might cover this part of the map, if you gave a vaccine, that cover that has the obsessive strain plus Omicron, you might cover this part of the map. But what you really want to do is what vaccine can we give, we'll give you the cover the whole map. And so what we do is that we look at people's antibody levels against the map and then becomes 3d. So if this is a person, and the inflection point, meaning how high it is off the map is their antibody levels against that part of that space in the map. Then you can see that antibody levels are really high in this space, which is over here, and really low in this space, which is over here. And then after you boost somebody what you'd want to see is that the entire map goes up meaning all their antibody levels against the whole map increases but it also flattened. So it increases across the whole map not just across one spot.

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And so using that tool, we can identify spaces on the map where you might be at risk. And then we can also look and see what happens after we boost people in infected or uninfected people. And we can see, does that boost from baseline to say they 29? After boost? Does it raise the map the way you want it to against all these inflection points? And does it flatten it so that you know you're covering the whole known landscape of what we call antigens or variants. And so that's sort of the science that we use to pick influenza vaccines every year. And that's how we're going to develop new vaccines for COVID, which hopefully, again, will go where the variants going, and not just where it's been. So by Valent, vaccine combinations do appear to offer serologic advantage as well as effectiveness. And they do flatten that landscape very nicely, more than if you just gave the original vaccine or you relied on your existing immunity. And because you can give, say, a beta vaccine that doesn't even have the original vaccine in it, and still boost very well against the original virus, probably future vaccines won't have prototype or the original vaccine sequences at all. And then lastly, hybrid immunity is probably the thing that we need to look at a little bit more closely because it offers the most broadly protective and durable immune responses. So we really need to understand why that is. It's probably related to cellular immunity. But I think understanding that it's really going to help us to make better generation vaccines in the future. And again, do our best to cover that known antigenic landscape. So I'll stop there and leave some time for questions.

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Hey, thanks so much. That was that was really interesting and very science heavy, as you had said ahead of time, and really points out how complicated and how far we've come and really such a short time of research, you know, even though the pandemic has seemed long, you know, living it scientifically, it's, it's, it's very, very short. Right.

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So very short, very.

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So we're open for questions, if anyone has a question they want to put into the chat. I was curious if what's happening in China now changes anything in the thinking of having and my knowledge of this is, is really sort of popular press, not science knowledge, that if there's a large population of naive individuals, who now you know, because of policy changes, will presumably have a sort of a general exposure without the same kind of reactions that we had originally, in our first part of the pandemic. Does that? Does that alter your thinking about the evolution of the virus?

33:30
Yeah, I think having a giant population of naive people who've never been infected, is hugely problematic for lots of reasons. One, because they don't have hybrid immunity. And we know that the primary just getting vaccinated alone doesn't give you the best protection against some of the newer strains, you know, BQ 1.1x, PB one, if you've never been infected, the antibody levels we're seeing against those strains, even with the update of vaccines just aren't great. And so that I think that that partially might explain sort of the huge wave of infections they're seeing in China, because they did such a good job of blocking down, they really curb transmission a lot. But then they that resulted in, you know, people who were vaccinated but never infected. Also having a huge population of uninfected hosts, and anytime you have populations of people, where large numbers are getting infected, that speeds up the ability of the evolution of the virus because every time a virus infects a person, it evolves. It has to be in a person, first of all, and so the more people get infected, the more evolution you're going to see, the greater the possibility that new branches of viruses may emerge. I hope it doesn't happen, but it certainly has especially with influenza. And so, you know, it's definitely something that's concerning

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I think a common question we get as infectious disease people, which I'm sure you get more than I do is, you know, what will be the standard? Will it be an annual booster? Will it be? Do you have a prediction of what? Where we'll end up?

35:30
Right now? It's going to be annual, I'm pretty sure they're not going to. Yeah, make us get boosted every six months, like we did in the first couple of years. And it'll be annual, I suspect for at least the next three to five years. And then we'll sort of see what happens. You know, since we have their seasonal coronaviruses, and we don't develop vaccines against those because they rarely cause pneumonia, and hospitalization. And so if as the virus evolves, sometimes to continue to be very infectious. It loses some variance. And so the thought was that over the next 10 to 15 years, who knows how long that as SARS Coronavirus to evolve, that that would in fact happen as well. It hasn't yet. But if if it does, then it may be that sometime in the future in the next five years or so we won't be to keep vaccinating people, because they'll have enough pre existing immunity to prevent severe infections and the virus will be potentially less virulent over time.

36:41
And then, just before we switch to the case, we do have one question that came in if a person who's never had never been vaccinated, but now it would consider vaccine with the initial vaccine in years to come not be the original initial vaccine. Do you anticipate a different primary series?

37:03
Yeah, um, so I don't think obviously, that that has not been updated yet. The primary series is still the original vaccine. But I I suspect that that will be updated this fall that the primary series will be different. Yeah.

37:23
All right. Well, thanks very much.

[End Transcript]