in Committee discussions in general. However, he's not authorized to participate in the Committee voting process.

Dr. Paula Annunziato of Merck will serve as the industry representative to this Committee. Industry representatives are not appointed as special government employees and serve only as non-voting members of the Committee. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. An industry representative on this Committee is not screened, does not participate in any closed sessions if held, and does not have voting privileges.

Dr. Jay Portnoy is serving as the acting consumer representative for this Committee. Consumer representatives are appointed as special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

Disclosure of conflict of interest for guest speakers follow applicable federal laws, regulation,

currently in.

And at that time, the influenza A strains that were recommended were an A/Guangdong-Maonan/SWL1536/2019(H1N1)pandemic-like virus for egg-based vaccines and an A/Hawaii/70/2019pdm09-like virus for cell and recombinant vaccines. The Committee also made recommendations for the H3N2 strain, an A/Hong Kong/2671/2019-like virus for egg-based vaccines and a A/Hong Kong/45/2019(H3N2)-like virus for cell and recombinant vaccines. The Committee recommended a B/Washington/02/2019-like virus for the B component of trivalent and quadrivalent vaccines. This is a B/Victoria lineage virus. And the Committee finally recommended an influenza B for quadrivalent vaccines containing the above three vaccines, and this was a B/Phuket/3073/2013-like virus from the Yamagata strain.

Now, last week the WHO met and made recommendations for next winter's Northern Hemisphere influenza season and the vaccines that would be made for that season. Now, the WHO recommendation I'll remind people -- this is a consultation that includes

all of the WHO collaborating centers, of which CDC is one. It includes the WHO central regulatory labs of which CBER is one. But these recommendations are just that. They're recommendations, and each country must recommend the vaccine composition for the vaccines that are licensed in that country. And that is what the purpose of the VRBPAC discussion today is, for the U.S. licensed vaccine.

But last week these were the recommendations that the WHO made for next year's Northern Hemisphere season. For influenza A, they recommended an A/Victoria/2570/2019pdm09-like virus for egg-based vaccines and an A/Wisconsin/588/2019pdm09-like virus for cell- and recombinant-based vaccines. The recommendation for the H3N2 component was an A/Cambodia/e0826360/2020(H3N2)-like virus, and the Committee recommended an influenza B/Washington/02/2019-like virus as the B component for trivalent and all quadrivalent vaccines. This is a B/Victoria lineage virus. And finally, for quadrivalent vaccines containing the above three

viruses, the Committee recommended a B/Phuket/3073/2013-like virus. So this is what the WHO recommended last week.

So the Committee discussion today, the VRBPAC will discuss which influenza strains should be recommended for the antigenic composition of the 2021-2022 influenza virus season vaccine in the U.S. Now, we'll have several options to consider as the discussion proceeds for influenza, and as usual, we will start with what the WHO recommended and then go from there. And after you hear all the data that went into that, the Committee will discuss and make recommendations.

But some of our options will be to recommend the A/Victoria and the A/Wisconsin strains for egg- and cell-based vaccines respectively that the WHO recommended or possibly recommend an alternative H1N1 candidate vaccine virus. Options for influenza H3 would be to accept the WHO recommendation of the A/Cambodia strain or make other alternative H3N2 candidate vaccine virus recommendations. For influenza

B, the options would be to consider the B/Washington strain or recommend an alternative candidate vaccine strain from the B/Victoria lineage or possibly a vaccine virus from the B/Yamagata lineage. And finally, for the fourth strain in quadrivalent vaccines, we could start with an option of recommending the B/Phuket strain that's the Yamagata lineage or alternative B/Yamagata lineage or even a vaccine virus from the B/Victoria lineage.

So the voting questions, we tried to simplify these as much as possible. We'd like to start with four voting questions, one for each strain, and I've listed them here. You'll see them a little bit later. But for the influenza A strains, we'll lump the recommendations for the egg- and the cell-based together, starting with what the WHO has recommended. And this would be for the influenza A H1N1 component of the 2021-2022 influenza virus vaccines in the U.S. Does the Committee recommend -- and these would be the A/Victoria/2570/2019 virus for egg-based vaccines, an A/Wisconsin/588/2019pdm-like virus for cell- or

recombinant-based vaccines.

Again, the voting question for the influenza H3N2 component would be would the Committee recommend the A/Cambodia/e0826360/2020-like virus? Third question would be for the influenza B component of trivalent and quadrivalent vaccines in the U.S., does the Committee recommend the inclusion of the B/Washington/02/2019-like virus? And finally, the fourth question would be for quadrivalent vaccines. Does the Committee recommend the inclusion of the B/Phuket/3073/2013-like virus from the Yamagata lineage as a second influenza B strain in the vaccine?

That should be it for the introduction. I can take questions, or we can -- I'll turn it back to you, Dr. El Sahly.

DR. HANA EL SAHLY: Thank you, Dr. Weir, for the introduction. Before we kick off the meeting with additional data presentation, if any of the Committee members has a question to Dr. Weir pertaining to (audio skip) raise your hand. And I see Dr. Cody Meissner asking a question. Dr. Meissner, please unmute

yourself and turn on your camera if possible.

DR. CODY MEISSNER: Thank you and thank you, Dr. Weir, for that presentation. So I see that it's only for influenza A H1N1 that has both a cell-based strain and an egg-based strain. And I assume that means that for the other three -- for the other A and the other two Bs they grow equally well in egg-based vaccines as well as cell-based vaccine. But the question, how is it determined that the protection from an egg-based vaccine is equivalent or better than immunity induced by a cell vaccine or at least equivalent? Do you look at serologic response in individuals? Thank you.

DR. JERRY WEIR: So to answer the first part of your question, yes, I think that is the assumption you can make is that one virus for the H3 is good enough for both egg-based as well as cell-based vaccines. I think last year we had a different egg-based and a different cell-based H3 component. But the answer to -- the more extensive answer you will hear from Dr. Wentworth, and you sort of guessed correctly.

What you will hear is data showing how well these different candidate vaccines cover and whether the candidate vaccine is made in eggs or made in cells and how well they cover viruses, both circulating viruses -- and you'll also hear how well these viruses are covered by sera from recently vaccinated individuals. So David will go through this all in great detail about why the selection of each of these virus strains was made.

DR. CODY MEISSNER: Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Weir. I do not see any additional questions right now, so it's my pleasure to introduce Dr. Lisa Grohskopf. Dr. Lisa Grohskopf is the associate chief for policy and liaison activities, Epidemiology and Prevention Branch, the Influenza Division at the Centers for Disease Control and Prevention. She will be doing a U.S. Influenza Surveillance overview. Dr. Grohskopf.

U.S. SURVEILLANCE

DR. LISA GROHSKOPF: Thank you, Dr. El Sahly, and good morning, everybody, and thanks for the chance to be here today. So I'm going to be presenting an overview of U.S. influenza surveillance, largely focusing on the current season, '19-'20-'21. And I'll just get started here with the next slide.

Before getting started with the data, I just wanted to thank our CDC Influenza Division Surveillance team led by Lynette Brammer and Alicia Budd. These are the folks that put together the FluView report that's posted on CDC's webpages every week. I don't myself work in surveillance, so I'm fortunate enough to get to present their data every year. And I'm greatly grateful for them in assistance in getting these slides together, as well as everything they do on a regular basis.

So just to start out with the U.S. influenza surveillance for the 2020-21 season, just to give you an overall orientation, the data that I'm going to present are from the most recent CDC FluView report. These are data that are posted every week, generally on

Fridays. The reports that these data are drawn from are for surveillance week 8. This is the week ending February 27, 2021.

I'm going to start out with virologic surveillance. These data come from influenza positive test results that are reported to CDC weekly by the National Enteric and Respiratory Virus Surveillance System Labs and also WHO surveillance labs that are located within the United States. These comprise about 300 clinical laboratories and about 100 public health laboratories. And the results that are reported to CDC are here, depicted in two separate graphs. The public health laboratories are on the right and the clinical laboratories on the left.

One thing I do want to point out is that for ease of viewing I have made these graphs the same size. However, if you do look at the scale on the Y axis, that shows the number of specimens that were -- if you're looking at the left-hand Y-axis -- the number of specimens, the scale is different. It goes up to 500 on for the clinical laboratories and up to 100 for the

public health laboratories because there are fewer specimen. So just keep that in mind that the bars that you see on the graph are not proportionate to each other.

Clinical laboratories by and large submit data that are divided into flu A and flu B. You'll see that the flu A isolates on the left-hand graph for the clinical laboratories are represented in yellow and flu B are in green. And one main take-home point here is that, overall, the number of specimens positive that broke down into A and B are relatively small this season. Typically, those of you who've seen these presentations or looked at the data before -- typically, we have nice sweeping peak that goes up much higher in that graph by this point in the season. Flu season's generally peaking in activity sometime in January or February. But overall, our number of positive specimens is low.

Another thing to draw your attention to on the public health lab -- sorry, the clinical lab graph -- again, the one on the left -- is there's a black line

that sort of runs close to the X axis but just a little bit above it. That represents the overall percent of specimens positive by week. This has been very low so far this season. Right now, it's about 0.1 percent for surveillance week 8.

On the right, we have the public health laboratory graphs. This has a few more colors in its wedging mainly because public health labs generally do split out the influenza A viruses by subtype, H3N2, H1N1, as well as the B viruses by lineage. But considering the fact, then you can see that overall the numbers are small, and again, remember that the scale of the X axis in this graph is lower than it's a smaller scale than the clinical laboratory graph. Again, the take home message is overall the number of positive isolates has been rather small for the season so far.

Apologies, I skipped a slide there. Okay. So next, we're going to move on to a couple of slides that describe U.S. ILI activity. These slides both come from ILINet, which is a network of about 3,000 out-

patient provider facilities that report weekly to CDC the percent of outpatient visits that are for influenza-like illness, or ILI. Now, this is a symptom-based definition. It is not a laboratory confirmed definition. So it's basically defined as fever, plus cough or sore throat. It is not something -- the data that you're going to see here, basically what I'm trying to say, does not reflect laboratory confirmed flu. It's a symptom-based definition.

So again, similarly to the last slide, we have calendar week on the X axis. We have percent of visits for ILI on the Y axis, and a number of different seasons are represented. The season that we're currently in right now, 2020-21, is the line superimposed with the red triangles. The horizontal black line that you see across the graph represents a threshold of 2.6 percent, which is calculated from the percent of visits for ILI during the previous three seasons during non-influenza weeks. So that's what we refer to in this system as the national baseline, and it's at 2.6 percent for this season.

So take-home point here is that for the current season -- again, the line superimposed with the red triangles, 2020-21 -- we are below the national baseline so far throughout the entire season. Considering HHS regions, the regional data is also below the national baseline. And this is lower even then -- if you look just above the current season line, a little bit above there's a brown line that represents the 2011-12 season, which was a season that was largely noted for having relatively mild influenza activity. We're even below that with this system.

So this is data from the same system. I think it's about 65 percent of the ILINet providers report data for a percent of out-patient's visits for ILI that are broken out by age group. And here you see that data, and there are actually two seasons here. The peaks that you see on the left side of the graph are from the '19-'20 season, and then the righthand half of the graph approximately is the '20-'21 season. So it gives you an idea of comparison with last season.

But these are data broken out by age group.

Zero to four is the youngest age group. 65 plus is the oldest age group. You can see that we see relatively flat activity through the 2020-21 season so far through the righthand part of the graph. There is a slight trend sort of slightly decreasing activity in the three older age groups, those other than the zero to four age group, if you look at about the last seven weeks. But overall, low activity.

Next, moving on to influenza associated hospitalizations. This comes from a network called FluSurv-NET. Normally, we have a chart for this season with the estimated cumulative hospitalization rates by the accumulating calendar weeks generally broken down by age group. FluView has not been producing that so far this season mainly because the activity has been so low. But what this system does examine is hospitalizations associated with lab confirmed flu.

The numbers have been quite small. Between October 1st, 2020 and February 27, 2021 -- that's again week 8 for surveillance week -- 14 states reported a total of 193, which is quite small, laboratory

confirmed influenza hospitalizations. This represents an overall cumulative hospitalization rate of 0.7 per 100,000 population, a bit too small for really meaningful breaking down by age groups, so hence no figure. This is lower than any season since routine collection of data for this system began in 2005, including, again, for reference, the 2011-12 season for which the rate at this timepoint was about 2.3 times higher.

The next two slides go into mortality data. This first one is from the National Center for Health Statistics, and these are the percent of deaths coded as being due to pneumonia and influenza or COVID-19. These are death certificate data, so this is not lab-confirmed flu data. So this would be deaths that are listed on the death certificate as being due to pneumonia, influenza, or COVID-19. Those of you who look at this data periodically, or who have seen these presentations before, know that in previous seasons this has generally been reported as pneumonia and influenza, rather than the addition of COVID-19.

However, at about week 10 last year, if you look to the far right on the graph -- about week 10 of last year was when we began -- the system began adding COVID-19 coded deaths as part of routine reporting.

So there are a number of seasons represented here. You'll see throughout the graph a pair of undulating black lines. One of these is the seasonal baseline, which is an estimate based on modeling data from the previous five seasons of what we might expect to see in terms of percent of deaths coded as being pneumonia/influenza. 1.645 standard deviations about that is what we call the epidemic threshold. So if you look off to the left, that starts out with the '16-'17 season, you can see -- actually the '17-'18 season -- the redline which represents the percent of deaths that were due to, in that season, pneumonia and flu only -- or pneumonia and influenza coding only. You can see that the red line broke quite a bit.

As you go across the graph, you see about week 10 of last year quite a bit of surpassing of the baseline by that red line. To sort of put things into

perspective as far as the relative proportion of deaths that are due to pneumonia and flu as opposed to COVID-19, some colors were added to the graph. Yellow represents pneumonia/flu coded deaths, and the blue patches represent COVID-19 reported deaths. You can see that for this current season the majority of those deaths are reported as being -- on the death certificate as being related to COVID-19 rather than pneumonia/influenza.

This slide is pediatric mortality. Pediatric deaths associated with laboratory confirmed influenza have been reportable in the United States since 2004, and this graphs shows by calendar week the number of deaths hitting this definition for the last several seasons, beginning with the 2017-18 season on the far left. For the 2020-21 season so far within this system, only one pediatric death has been reported so far for this season.

So just an overview on influenza activity domestically for this season, U.S. influenza activity for 2020-21 has been low so far. The percent of

influenza specimens testing positive as reported by the clinical laboratories unusually low, again, 0.1 percent for the most recent reporting week. Influenza-like illness, ILI, activity has been below the national baseline, and the cumulative hospitalization rate reported through FluSurv-NET, 0.7 per 1,000, which is again the lowest since 2005 and even lower than the 2011-12 season.

The causes for this, the ideologies for this are likely multifactorial and could well be related to COVID-19 mitigation strategies such as use of masks, social distancing, school closures, and also things related to travel such as people travelling less and also, in some cases, restricted travel. Importantly, it's not possible to predict whether this is going to continue to hold for the rest of the year, and it's also not possible to predict on the basis of these data the extent and timing of influenza activity for 2021-22, next season.

Now, I just have a very, very brief update on vaccine effectiveness. For the last few years, we've

also presented in this talk updates on flu VE from the CDC networks. The update this year is quite brief. In fact, this is the only slide we have.

Due to the very low activity within the United States and, of course, by extension within the CDC VE networks this season, there are no interim VE estimates available. The CDC networks continue to collect data as it comes in and to monitor activity. However, there is no interim estimate available from any of them, and estimates, as far as being available later in the season, are completely dependent on having sufficient influenza activity within the networks in order to be able to calculate a VE. So that is all I have for my talk. Thank you very much for your attention.

DR. HANA EL SAHLY: Thank you, Dr. Grohskopf, for this presentation. As the Committee members raise their hands for those who have questions so we can (audio skip). I have a quick question to get us started. Did we see any changes in the vaccine coverage this year in terms of the uptick of the flu -- the seasonal flu vaccine?

DR. LISA GROHSKOPF: There is ongoing preliminary data on coverage that's being collected and posted week by week on FluVaxView, which is another CDC webpage. There are coverages estimated for different populations using different surveillance systems, and there are some new data sources that are being used this year. Overall coverage, depending upon the group that you look at, looks about on par with last year. There looks to have been in some populations -- some age groups fairly high demand in the beginning of the year but then sort of leveling off later on in the year. There are also some differences in coverage by race and ethnicity in some of those systems. But I would say overall not an enormous different between -- some groups showing slightly lower, some slightly higher depending on the surveillance system used in which population group.

DR. HANA EL SAHLY: Any indication the lack or the tremendous decrease is actually partially related to public health resources --

MR. MICHAEL KAWCZYNSKI: Sorry, Dr. El Sahly,

we need you to move the phone closer to you. We can't hear you.

DR. HANA EL SAHLY: Oh, okay. So any indication that the decrease in the number of cases is at least partly related to a lot of our public health efforts being directed elsewhere?

DR. LISA GROHSKOPF: That's a good point. I think one thing that was noted early on in FluView reports and also in other surveillance systems was that one thing to be considered is that, particularly at the beginning of the season -- earlier in the COVID-19 epidemic, one might expect that testing practices for flu might have changed. One might surmise that it was possible that people might not have been going out to get tested. But one thing that is interesting even in the face of all that is that of the specimens in the reporting on testing that CDC has seen, for example in the virologic characterization data that was reported on the first slide I presented, the percent of tests that were positive is very low, which is also something important to note that one might not think would be

influenced, say, based on testing practices or people's likelihood of getting tested or clinician behavior.

DR. EL SAHLY: Okay. Thank you. Dr. Michael Kurilla, please unmute yourself and turn your camera on.

DR. MICHAEL KURILLA: Thank you, Hana. Lisa, related to the testing, I'm wondering from the ILI standpoint it would seem to me that a lot of the routine things of people, you know, in traditional flu seasons calling their doctor and going into their office, that's not happening. I would also think that most people, if they had flu-like symptoms or influenza-like illness, they'd be worried about COVID, and it may be that they'd get a test for COVID. And if it's negative, they just feel so good they don't bother about anything else. I'm wondering how much dual testing for COVID and flu is going on so that in people who are symptomatic, if they're negative for COVID, we actually know whether that's flu.

DR. LISA GROHSKOPF: That's a good question, and I don't -- I can try to get more information on

that during today. I don't know off the top of my head about the prevalence of dual testing, although one would imagine it would be happening. The surveillance team does note that the ILI numbers should be interpreted sort of cautiously, again, given the possibility that the ability to detect ILI has been influenced somewhat by the ongoing pandemic and testing practices. But as far as dual testing, I can try to get more information about that today if it's available.

DR. MICHAEL KURILLA: Thanks.

DR. HANA EL SAHLY: Thank you. Dr. David Kim, please turn your camera on. Dr. David Kim.

CAPT. DAVID KIM: Thank you. Other than the -- for the biologic surveillance, other than the numbers that were much lower than the years past, did you notice anything different during the current season regarding strain predominance or any sort of pattern that you saw compared to the years past? I realize that the comparison can't be directly made but at least some preliminary analyses on that.

DR. LISA GROHSKOPF: Good question. FluView normally does report out antigenic and genetic testing data based on the samples that are tested and has not been doing that so far this season simply because the sample size has been so small. As far as further detail on that, I'm think I'm going to defer to Dr. Wentworth to see if he has any further information on that. But again, it has been highly unusually this season in terms of the low number of activity -- the low amount of activity, the low number of positive specimens. It's just a very, very, very small sample size. It's a good question.

DR. HANA EL SAHLY: Thank you. Dr. Paul Spearman, please turn your camera on.

DR. PAUL SPEARMAN: Thank you and thanks for that presentation. You know, I was so struck by the low numbers, especially the graphs for pediatric deaths where there doesn't even look like there's any season at all. It's amazing, and your discussion of the multifactorial nature really leads me to wonder what are the real causes of that. I would have -- you could

have predicted that, you know, masking and some distancing and avoiding large gatherings could affect the flu epidemics.

But I would have expected this degree, and it's just -- it's such an amazing finding at the same time when those measures were not really preventing the large winter uptick in COVID cases. So it's just -- is there -- or will there -- I don't know if anyone can really answer this, but will there be ways of teasing out what looks like it works much better than a vaccine to prevent flu? Can we really do this, you know, in an effective way going forward? Thanks.

DR. LISA GROHSKOPF: So I imagine that there will be future examination of those questions, although I'm not really certain about the specifics of kinds of studies at this point. I think it's also important to consider that flu seasons do vary, and we do sometimes have seasons that, you know, barely break the epidemic threshold. For example, 2011-12 was one of those seasons. This has definitely been lighter.

So I think in the space of all this, it's

important to also consider the fact that flu is still unpredictable, and we really don't know how it's going to behalf in the future. That being said, it does seem like something happened this year, and there were changes in behavior that warrant further investigation as far as the degree of their impact and how they can be used in the future.

DR. HANA EL SAHLY: Paul, I think this question came up in different circles, the differential of the effect of the social measures against flu versus SARS-CoV-2. I mean, the main difference that we also have to factor in is the differential in susceptibility. Anyone older than one year of age has a degree of immunity against one flu or another but nothing against SARS-CoV-2, so that also changes the effectiveness of the approaches. Dr. Mike Levine. Dr. Levine, you're muted.

DR. MYRON LEVINE: Can you hear me now?

DR. HANA EL SAHLY: Yes, sir.

DR. MYRON LEVINE: Thank you. My question was very similar to Paul Spearman. The striking virtual

disappearance of influenza is so notable, and in theory it might -- if the surveillance division has data, might be a way to tweeze out the role of kids not going to school, the role of masking, the role of social distancing in certain subpopulations. But one also has to wonder whether with the very widespread SARS-CoV-2 infections is it possible that the innate immune response, interferons, et cetera, to SARS-CoV-2 has somehow also in some way being responsible for less influenza. Whatever the reason, it's going to stimulate this question again and again, and there's been so much in the public arena whether masks work or not, whether schools are involved in transmission. And maybe the answers in part for COVID can come from figuring out what happens with flu.

DR. LISA GROHSKOPF: Definitely this season will yield a lot of important research questions for consideration. Yeah.

DR. HANA EL SAHLY: Thank you. Colonel Andrew Wiesen.

COL. ANDREW WIESEN: Thanks, Lisa. It was a

great presentation. I just had a question about how much effort has gone into the potential data misclassification. I mean, you mentioned it, and certainly it's true for deaths that there's a large portion of the COVID deaths that also had flu. When you take all the flu cases out, it's like half, or it's a large proportion. And that's where we have the best information, right, because if you die, you're going to likely get tested for flu as well as COVID.

The testing was brought up by a previous speaker. A lot of times people just get a COVID test, and if that's positive or negative, they don't follow up. And so while I agree that the social mitigation is almost certainly somewhat responsible, I think there's a lot of data misclassification. And I think that flu, while suppressed, is certainly not as suppressed as we might otherwise think because people simply aren't coming in or getting tested for it.

So I wonder how you might approach that issue of trying to determine how many cases could have had either dual or misclassified -- it says it was COVID

because they were positive for COVID, but they were actually a flu case too. Or maybe flu was the predominate reason for their systems, hospitalizations or otherwise, because I don't want to oversell the suppression of flu this year when it's really tough understanding now when you look at the death count lately has not come down nearly as fast as the case counts and hospitalization counts. And part of me wonders how much of that is just residual because this would have been peak right now the last couple of weeks. This would have been peak deaths for flu season, too. So how much of that is actually flu still that's just being classified as COVID and is not. So just your thoughts on that.

DR. LISA GROHSKOPF: I think based on my understanding of the surveillance systems that -- for example, ILINet and also the NCHS data -- those systems don't access testing data, so NCHS receives, for example, data from death certificates. And of course, you know, we know that there are limitations to death certificate data. It's based on coding, and those

individuals may not have been tested.

A simple answer would be, you know, trying to review all of those charts. I don't know about the feasibility of doing that within this particular system. It's possible that there are other studies that are examining that, but within these networks I don't know if we can get at that data. I think those are all important points, though. Some of the routine CDC flu surveillance examines lab-confirmed disease. For example, pediatric mortality the hospitalization system does. But for some of the systems, ILINet and NCHS, we just don't have testing data.

DR. HANA EL SAHLY: Thank you. Dr. Cody Meissner.

DR. CODY MEISSNER: -- presentation. Thank you for that interesting presentation. One more point I wanted to add to the discussion that Paul and Mike raised is Respiratory Syncytial Virus. And we have had almost disappearance of bronchiolitis at our hospital and, I think, many other hospitals as well. So we think of RSV hospitalization as primarily among infants

and young children who are less than 12 months of age and maybe less than 24 months of age, but most of them are in the first year of life. So, I mean, that leads me to believe that the influenza results that you're reporting are probably real in terms of a reduction because it seems to be all the respiratory viruses are down. And somehow, it makes it harder to say not going to school accounted for a reduction in RSV hospitalizations because those children don't go to school who are most likely to be hospitalized. So I think there's something more here that I'm not sure we fully understand. Thank you.

DR. LISA GROHSKOPF: I agree. There have definitely been a lot of different behaviors that were introduced and encouraged by -- including some that maybe we don't talk about as much. People may be washing their hands more often, may be using more sanitizer. It's really hard to know. I think one thing that comes into the CDC recommendations for preventing flu in addition to vaccination are everyday preventative activities, which in our communication

materials point out, you know, these might help you prevent getting sick from other respiratory virus as well, so things like, again, washing your hands, avoiding sick contacts. And one could guess that probably there are more of both of those things going on this year in addition to the fact that we're just not as mobile as a population.

DR. CODY MEISSNER: Thank you.

DR. HANA EL SAHLY: Thank you. There is time for two more questions, and the first is coming from Dr. Amanda Cohn.

DR. AMANDA COHN: Hi, Lisa. Thank you. I think you actually just responded to part of the comment I wanted to make, which is I think it's not only the social distancing. But I also wonder the contributions of overall travel changes over the course of the pandemic, both international and domestic. And I think that is -- you know, I think it's likely a combination of all of these factors, but I think that will also be interesting to evaluate in the future.

DR. HANA EL SAHLY: Thank you. And the last

question is from Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you. Just a follow up comment to Dr. Meissner's comments and that is with regard to the young children who are not in school. A lot of them, I think -- I'm trying to remember, but somewhere I had read a long time ago that about 70 percent of children in the U.S. in that age group are actually in childcare that is outside the home in aggregate settings. So I think that a lot of those have been closed as well. And so these children are not coming in contact with children outside the home.

DR. LISA GROHSKOPF: Yeah. Good point.

DR. HANA EL SAHLY: Okay. Thank you, Dr. Grohskopf and Committee members for this discussion. Next is Dr. David Wentworth. Dr. David Wentworth is the Branch Chief, Influenza Division, Virology Surveillance, and Diagnostic Branch of the Centers for Disease Control and Prevention. Dr. Wentworth is going to give us a presentation on the global influenza virus surveillance and characterization. Dr. Wentworth.

GLOBAL INFLUENZA VIRUS SURVEILLANCE AND CHARACTERIZATION

DR. DAVID WENTWORTH: Thank you very much. I have a lot to cover. I will move rather quickly but hopefully easy enough to follow for everybody. I just put together a brief outline to remind everybody what we'll be talking about.

We're going to do an overview of the WHO vaccine consultation meeting and the recommendations that Jerry went over. We'll talk a bit about the influenza activity, A(H1N1)pdm09 viruses, and I'll describe the major highlights. If you recall, I covered this in more depth in the 2020 VRBPAC meeting, and while the recommendation for the H1N1 is an update for the Northern Hemisphere 2021 and 2022 season, it is the same as the Southern Hemisphere recommendation for the 2021 season that's upcoming.

For the H3N2 viruses, I'll be discussing in greatest detail today of all the subtypes, and that's

an update to the recommendation. And for the B/Victoria lineage viruses, I will also cover some aspects. The recommendation remains the same, but we have seen the expansion of a previously small kind of subclade of viruses that I'll point out to you that we're keeping an eye on for future. And with the B/Yamagata lineage, I'll be very brief. This lineage is really impacted by a number of things, and there's not very many viruses around. And we can discuss that in question and answer if there's time. Okay.

So for the meeting, this really results from year-round surveillance conducted by the GISRS or the Global Influenza Surveillance and Response system. We have all the members of the GISRS including the WHO collaborating centers -- there's six, and the CDC is one of them -- National Influenza Centers -- there's more than 140 around the globe -- WHO essential regulatory laboratories, like the FDA CBER; WHO H5 reference laboratories, and it's supported by many countries and partners, including GISAID, which is a global influenza sequence sharing database system

that's been taken advantage of for the SARS coronavirus pandemic as well. So the meeting was held on February 17th to the 25th. It was a virtual meeting with a time difference of 17 hours among the various participants.

I was one of the chairs, along with Dr. John McCauley, and we had the other advisors and directors of the WHO CC's and essential regulatory capacities as voting members, as representatives for their corresponding WHO CC and ERL. There were 57 observers from WHO CCs, WHO ERLs, academia, H5 reference laboratories in the veterinary sector, and we also had experts from WHO regional offices and headquarters. The recommendations in front of you is for the Northern Hemisphere 2021 to 2022 season for quadrivalent -- sorry, I'm getting a call.

MR. MICHAEL KAWCYZNSKI: Dr. Wentworth, we lost your audio. Dr. Wentworth, we lost your audio. Hold on a minute. We're going to take -- just give us a second here, unless it's just me, but I believe we lost audio. Somebody else confirm -- studio, give us a moment. We're going to take a quick -- like a one-

minute break. We're just going to put a note in here so he can dial back in.

Your audio -- there you go. You've got it. It's all right -- while he's reconnecting -- not a problem. Sorry about this, everyone. We're just going to take a momentary little technical break while Dr. Wentworth dials back in. Not a big deal. It does happen. Here he comes back in. No problem. He's coming in now. Happens to the best of us. I see him dialing in now. Come on. We can do it.

So those of you -- thank you online for watching or 165th VRBPAC meeting. While we're waiting on Dr. Wentworth to connect his audio, a good time to grab a cup of coffee. I'm just going to call him in directly. I wish I knew how to juggle and keep you all entertained just for a moment, but I'm waiting for Dr. Wentworth to call me in. Put that up for a second here just while we're waiting.

Those of you -- I love our members. They're having a little fun with me. They're, like, doing puppets and all that other stuff. There you are. It

was funny. I know what you did. You clicked on the arrow, and you clicked "disconnect your phone." It was sort of a little humorous. That's all right. We're all back, David. Take a deep breath.

DR. DAVID WENTWORTH: I apologize wholeheartedly.

MR. MICHAEL KAWCZYNSKI: That's okay.

DR. DAVID WENTWORTH: I keep getting messages now, and it wasn't connecting me back to the conference. I apologize to all the listeners.

MR. MICHAEL KAWCZYNSKI: So take a deep breath and pick up where you left off.

DR. DAVID WENTWORTH: Basically, these were the recommendations. The ones in blue were the new viruses being recommended. And I did want to point out one thing, that the cell viruses, even when they have the same name, are different recommendations than the egg viruses. The egg viruses have been isolated in eggs, and they have sometimes different amino acid changes in order for them to replicate in eggs.

And so we call that an egg-cell pair. So for

example, the Cambodia is an egg-cell pair. The egg virus is slightly different than the cell virus, and the manufacturers know this. And it's listed specifically on the candidate vaccine viruses that are available through the WHO website. That's true for all egg and cell viruses. This is why sometimes they have different names. We weren't able to get an egg-cell pair, but we have something similar. Okay.

I might want to stop using that arrow if I'm going to cause trouble with it. Okay. So these are the number of specimens processed by GISRS, and what you can see over the past two seasons from 2018 to 2021 the black line there is the 2020 season. And then towards the end of that year, you know, as you get to weeks 51 and 52, 53, it starts to decline. And then that picks up again for the next year in the beginning of the year. And so that's a pretty normal looking number of specimens processed, and so these were tested for influenza.

To go back to that discussion we had earlier, there was a lot of specimens being processed but not

very many percent positivity, and that's what Dr. Grohskopf mentioned. So the percent positivity was way down, and this is real. Okay. I won't belabor this graph because you can see it, but it basically came down as SARS emerged and then became a pandemic in the beginning. So if you follow the red line, you see that sharp decline when all the mitigation factors were coming in at the end of our last flu season. Okay.

This shows you the global circulation of viruses, and, again, it just illustrates that we didn't have a lot of viruses to work with. You can see that on the Y axis of these charts there's thousands on the chart on the left from the 2019 to 2020 season. In the chart on the right, the 2020 to '21 season, these are in the hundreds. But they are there, and we can still analyze them. We can't ever analyze 4,000 viruses for each group anyway, so we do have representatives to analyze.

And this is showing influenza activity globally with the lighter colors being zero to 10 percent. And as you can imagine, basically most of

this was low, and we did see some regions around the globe, like Western Africa, that had a little bit higher influenza incidence. Now, countries and areas as well as territories that shared viruses with WHO CCs are lower than normal because they weren't able to isolate and characterize as many viruses. There were fewer viruses, and they also were very busy with the COVID pandemic. So that's kind of a double hit on what could be sent to WHO CCs. Many of the GISRS laboratories are the same around the world -- are the same laboratories identifying SARS-coronavirus-2, the cause of COVID-19. Okay.

So this is the percentage of influenza viruses by type and subtype, and what you can see here is they're both -- A and B circulated rather equally, with B viruses being 55 percent of the viruses, so predominating a little bit more. And for the B viruses, the B/Victoria virus is the one that predominated. So this other dark one here is the B lineage is not determined, but there's very few B/Yamagata lineage viruses circulating. And it's less

than 1 percent.

For the A viruses, the (H1N1)pdm09 viruses represented less than the H3N2 viruses. But this was regionally different. It's by country.

This shows how many viruses were genetically characterized by WHO CCs in this two regions of time, September 2019 to January 2020 and February 2020 to January 2021. What you can see is there is a reduction, and this timeframe is -- for the orange bars, you can see a bit of a reduction. But we were able to sequence a lot of viruses towards the end of our last season, so there was many viruses in this late spring, so after the last vaccine strain selection for the Northern Hemisphere.

And now, I'm going to turn your attention to (H1N1)pdm09, subtype influenza A viruses. This is specifically showing their activity. In the percent positivity, you can see we had some in North America and in Western Africa and a little bit Central Africa and in Asia.

Now, this is a similar chart to what I showed

you before, but now it's focused on H1N1. And so it's very low. It's the red line for 2021, and the black line for 2020.

Now, I'm going to focus your attention in on this phylogenetic tree a little bit. I know these are complicated, but it really helps us define what we're doing and why we're selecting what we're selecting. So at the bottom of this tree where I've placed the arrow, there's three substitutions there. They really form the main branch of all the viruses that have circulated for the last about three or four years. And what you can see as you go up this tree is continuing increase or evolutionary distance away from that bottom arrow.

And I have boxed two regions of the tree. So in this region here, this yellow box that I'm pointing to these amino acids, D187A and Q189E, those are at the base of this main subclade of viruses that we call 5A1. That's where the current cell-prototype vaccine is, Hawaii/70/2019. And so that's what we were vaccinated with last fall and winter.

And then the top of this tree, there's a

branch of viruses really breaking off at this N156K amino acid substitution in the hemagglutinin. And the new recommended prototype, I've put an arrow there -- was Wisconsin/588. And this is in this clade 5A2, so the red bar represents all of these viruses that are the tips of this tree. You can see all these little dots. Those are each individual hemagglutinin genes on every virus that was isolated.

And this tree is full of information. It's actually more than a phylogeny. It's an integrated dataset that also shows geography or phylogeographic. So the blue tips represent North America. Green would be Europe, and that's illustrated in this heat map, which starts on the very far righthand side. It starts in February 2020 and goes to November here. You can see that. And so you can also see when viruses were circulating and where they were circulating in that heat map.

Now, lastly, I'm going to focus your attention to some antigenic information, so how well these viruses are neutralized by sera to Hawaii/70, the

recommended cell vaccine prototype. And so that's shown in these two columns here. And what you can see is sera from Hawaii/70 will start back down and towards the bottom of the tree here. Sera from Hawaii/70 well neutralized all these viruses in subclade 7, those in subclade 5B, 5A1, and 5A.

So when you get to the 5A2 viruses, you see all these dark bands. These represent reductions from homologous titer between 16 and 32-fold or eight- and 32-fold, and so that's shown in this column here. I'll just drop that arrow down the column. And so you can see how poor this group of viruses reacts with that serum. And this is the newer emerging group of viruses where the new recommended prototype is. Okay.

This shows you the clade distribution from September 2020 to February 2021. And so as was mentioned we haven't seen a lot of influenza circulation or H1N1 circulation in particular, and we have a much smaller number of clades co-circulating in a few regions. We saw 5A1-187 viruses in parts of Europe and Africa predominating. We saw 5A2, these

ones with the 156K substitution in red, circulating in Asia and a few 5B viruses circulating in the United States and other regions.

Now, this slide illustrates the reactivity of viruses with their antisera to the antigens that are recommended for the Northern Hemisphere 2020-21 season. And so there's the cell recommended prototype, so antisera against that, or antisera to the egg recommended prototype, A/Guangdong-Maonan/1536/2019. And while part of the issue here is this period there weren't very many viruses if you use this cutoff of September 1, 2020 to January 31, 2021, so if we included viruses from the springtime, you'd get a lot more viruses. And we'd see a certain trend. Nonetheless, the few viruses that were able to be analyzed, 92 percent were considered like the vaccine, and there wasn't a huge difference between the egg or the cell in this reactivity pattern.

This slide is something called antigenic cartography. Jerry Weir mentioned that we would talk about this. And what this is, is the way to take these

HI tables or hemagglutination inhibition or virus neutralization tables where each virus is compared against the reference sera, against the homologous titer. They become very big tables of numbers. And this is a way to take it and map the data on two dimensions.

And so if we take antisera, for example, against, Guangdong-Maonan right here -- and that's represented by this egg-shaped dot -- that's where that antigen lives. If we take antisera against that, it reacts very well with all these blue dot viruses which represent viruses from the last 12 months. The grey dots represent viruses preceding that. And then if we take antisera -- so you can see this antigenic distance is pretty far until you get to this other egg virus here, A/Victoria/2570 egg. But it's now very close to all these red dot viruses.

And the difference between the blue and the red is -- one of the major differences anyway is this position at 156. So if it's an asparagine or an N, they're color-coded blue here, and they have a certain

antigenic phenotype. And if they're -- it just shows that one amino acid in blue can really dramatically impact the antigenic makeup of the virus. This is a very important antigenic region site assay.

So 156 is in red there, so you can see that. So this is data that I've been pointing at from the CC in London, the Francis Crick Institute, but this is also true from the CC in Melbourne. So you can see we all compare our data and see if we're having the same trends.

Now, this is looking at human post-vaccination serum analysis with H1N1 viruses, and I think this is -- I'll be pretty brief because of our time situation. But we're comparing the geometric mean titers relative to the cell propagated Hawaii/70, so that's this column here where we have -- and basically, people were vaccinated with Hawaii/70-like viruses. They were either vaccinated with Hawaii/70 if they got the cell -- like Flucelvax or the recombinant like Flublok. And they were vaccinated with Guangdong-Maonan-like viruses if they were vaccinated with an egg-based product.

So what you can see is a pretty good stimulation of the immune response from a lot of panels of sera, from 6- to 35-month-old up here at the top, to three- to eight-year-olds, nine to 17, the adults, 50 to 64 elderly, and 65 and older. And sometimes what you see is certain age groups still have good cross reactivity against a variety of viruses, and what we're doing here is I should have mentioned maybe more on the evolutionary tree. But we talked about the clades. This is clade 5A1, so this is a virus in clade 5A1 used as the antigen for the serum to inhibit. So it inhibits it very well.

Now, when we go to a 5A2 with these 156K viruses, there's poor inhibition, so there's much stronger reduction in the geometric mean titer. And when it's red, it's significantly reduced. So that's where we're seeing significant reductions in that group, whereas the 5Bs, which also co-circulated to a limited extent, do show cross-protection of this 5A1 vaccine or the sera from people that were vaccinated with the 5A1 vaccine. Same with the clade 3, which is

Idaho/7 and same with clade 7, which is Louisiana/01. And the difference you see here is primarily in the pediatric population which haven't seen very many influenza viruses or been vaccinated by very many influenza viruses. So this vaccine is basically likely stimulating memory that does cross-react with other clades.

And because there's been a lot of interest in the human serology at the VRBPACs, I've included another analysis just of a smaller subset so that you can see data a little differently than just statistically analyzed. And so here, I won't belabor this. We call these bubble plots, and what they're really showing is the pre-vaccination titer against each antigen versus the post-vaccination titer against that antigen.

And you can look at -- so, for example, kids, which I just pointed out before -- the young children, six to 35 months old, that vaccine does induce good immunity, about 80, not whopping but that's normal for younger kids. And it's not inducing lots of cross-

protection against these variant groups, particular this Wisconsin/588. Whereas the older adults, you can see that when you get vaccinated with this 5A1 vaccine you get a 171. You've moved all these people up. They have higher neutralizing titer, but they also have higher neutralizing titers to what would be considered an antigenic mismatch virus.

I think that's important to point out. You know, sometimes it's not as high as you'd like to see. But being vaccinated does help even a little bit against these more divergent viruses.

So to summarize the (H1N1)pdm09 viruses, they predominated in some countries in the Northern Hemisphere. This was in Africa, such as Egypt, Niger, Togo, in Asia, and in Europe. The HA gene sequences belong to 61A. That's the major uber-clade that I didn't even show you. That's all that entire tree basically. And there's a bunch of subclades in that tree, the clade 5A -- these are genetic groups is what we call subclades -- 5B that are co-circulating. And the majority of those now belong to this 5A clade, and

it's further diversified into two 5A subclades, the 5A1s and the 5A2s. And the 5A1s have these characteristic D187A chains at the base of that clade, and the 5A2s have these characteristic N156K chains at the base of that clade, along with these other changes that likely impact their antigenicity to a little bit lesser extent.

So for the ferret antisera to the reference (H1N1)pdm09 viruses like Guangdong-Maonan/SWL1536 from 2019, they will recognize many of the circulating viruses from this time period. However, they very poorly recognize the 5A2 156K viruses. In contrast, you know, the post-vaccination sera collected from humans vaccinated with 2021 vaccines reacted pretty well with all the 5A1 viruses but did show significant reductions in the geometric mean titers against viruses that represent those HA group of the 5A2. And then, for antiviral analysis very few were available in this period, but all of them were analyzed. And none showed reduced susceptibility to neuraminidase inhibitors or the PA inhibitor, baloxavir.

Now, I'm going to turn your attention to the H3N2 viruses. This is illustrating a number of H3N2 viruses detected by the GISRS, again, over the past few seasons from 2018 to 2021. And as you can see and we've discussed, there's not a lot of detection. It's good to have this in the information available though, so I'm sorry if it's belaboring that point.

Here's showing the more localized activity globally. You can see there was quite a bit of H3N2 in Western Africa and parts of Asia and then a little bit more modest activity in North America and Europe.

Now, this is illustrating the phylogeography of the H3N2 HA, and I walked you through that last tree. So it's the same set up where we have the various clades denoted by these bars along this very first column, and I've marked the two kind of most important clades because this is very busy to understand all of these trees, I know. But there's this clade here, which is known as the 2a.1b.1b clade. And I'll just call those 1b viruses because the name is getting very long.

And then these dark viruses that are named here represent reference viruses that we use in the human serology assay, and so we had those in the H1 tree as well. And those will be at the top of the columns of the human serology assays. So what we're doing for that human serology and for the ferret serology, really, is identifying key viruses that represent each of these major clades and testing those pretty extensively. And that's what we make our reference antisera for. It's also what we test the human sera with. And then we test, of course, all the other viruses that we have available against those reference sera from the ferrets, but we can't test so many viruses with the human sera. Okay.

And so, again, we saw towards the end of spring last year there were a lot of viruses circulating globally. In these columns here you can see, and they were in North America, Europe, Africa, South America. Okay. And so the vaccine prototype is in this group. It's this Hong Kong/70 -- or Hong Kong/45. I apologize. Hong Kong/45 and also the egg-

based vaccine is Hong Kong/2671 shown here.

The vaccine recommended by the WHO for the upcoming season is up in this top group here called the 2a viruses, so the 2a1b.2a viruses rather than a 2a.1b.1b virus, which is the other group. These are represented by viruses like California/55, Tasmania/503, and viruses from Cambodia, many in Southeast Asia. There was also a split off of this new group which really all start at this amino acid set. It's probably hard to read here, but I'll define it later. And that's a 193 change. And these existed in Bangladesh. They have a few more substitutions, and they are some of the most recent viruses circulating are these viruses here.

So this is how complicated the H3N2 genetic clade distribution of just the hemagglutinin gene was from February 2020 to September 2020. You can see all the various clades that were cocirculating with regional differences. For example, a lot of 3A viruses in Europe, many 2a1b.2a viruses, these bright green ones, in Asia and Southeast Asia, and many of the

2a1b.1b viruses, the dark green ones, also in China and other parts of Asia. And in the United States, we had kind of a mixed bag. And to remind you, the vaccine was in this 2a1b.1b group.

Now, it gets a little simpler with the bottleneck of the COVID-19 pandemic and all that was discussed earlier really dramatically impacting the number of different influenza viruses that we've been able to detect and the number of clades that are co-circulating. So in some ways, it's one of the easier years. Hopefully, we're not missing something. But the main viruses are really this 2a1b.2a clade and the former 2a1b.1b clade in the 180 clade in blue.

Now, when we look at the reactivity against the recommended Northern Hemisphere 2020 and '21 as well as the Southern Hemisphere 2021 seasons, you can see that the reactivity is a bit mixed. And for the CDC, for example, we had 63 percent were considered low reactors to the Hong Kong/45 cell antigen, which is shown on the left in the blue graphs. And overall, the total from, for instance, the Francis Crick Institute,

and VIDRL and the CDC where we had H3N2 viruses to look at, 44 percent are considered like the vaccine, and 56 percent were considered unlike or low to the vaccine is a better way to say it, with eight-fold or greater reductions. And with the egg vaccine antigen, this skews the percentage to the right and makes more of them considered eight-fold or low, reduced.

This is illustrating antigenic cartography again. So our Hong Kong/45 cell recommendation in the chart on the left is here. It's actually this dot here, and the Tasmania cell, for example, that new group would be here, as well as these new viruses in the HINT assay shown here in the yellow dots. These are the ones that have F193S. And on the righthand side -- this is again from our colleagues at the University of Cambridge using the HI data created at these different centers, for example, CDC on the left of VIDRL or Melbourne CC on the right. This Cambodia egg, which represents one of the new candidates showing here up in this region being able to react with many of these newer group of viruses.

Oh, Mike, that's not displaying correctly. I guess we'll just move forward. This was actually a detailed hemagglutination inhibition assay illustrating how the current vaccine reacts against -- oops -- how the current vaccine works against the viruses that are circulating recently. And it was poorly recognizing these viruses that would have been down here and how well the new recommendation would work. It's kind of a crazy presentation today. Sorry about that.

Here's the human post-vaccination serum analysis. Again, we're looking at geometric mean titers now against the Hong Kong/45 cell virus, which is the cell recommended candidate. And I won't walk you through all the panels because I've done that before. But these recent 2A subclade viruses, you can see they're the ones that are the lowest in all the panels, all the age groups, and have significant reductions, thereby illustrating their risk to humans with our lack of reactivity and cross-protection against those viruses.

This is illustrating, again, the bubble chart

showing -- you know, we can focus in on a couple here. Like, in the adults it's a little more interesting to look at. The pediatric population behaves a little more like a naïve ferret because they haven't seen very many viruses. So you can see this Hong Kong/45 vaccine in the Flucelvax did a good job stimulating immunity from 44 to 485 was the titer increase on average. So 80 percent had a four-fold rising titer or more. That's what this up arrow 80 percent means -- and were stimulating cross-protection to some extent. See, 126 against this quite new group that hasn't circulated in people before -- and stimulating good reactivity to these 3A viruses, which are antigenically very distinct. And that's true for Flublok, and it's also true to a certain extent to IIV4, which is an egg-based product.

So to summarize the H3N2 viruses, in most countries, areas, and territories reporting influenza A viruses, we saw both (H1N1)pdm09 lineage and A(H3N2) lineage subtypes. With regard to the phylogenetics of the hemagglutinin, the circulating H3N2 viruses from

this period all belong to the 3C.2a1b subclades, and I've shared these subclades in bullet points down here. There's the 1A viruses. I won't walk you through all those amino acid changes -- the 1B, the 2A.

And this 2A represents where -- so the 1B are the viruses where the vaccine that we've had previously was in this group, and the 2A is where the new vaccine is recommended to be. This is split into two subgroups that I pointed out, some more like the Tasmanian and Cambodia viruses. They both share this F193S and Y195F. Whereas the Tasmania and Cambodia viruses have those K171N substitution and those that were in Bangladesh and some other regions have the 159 substitution.

Importantly, I didn't show you the data, but both groups -- both these new groups share some substitutions in the neuraminidase gene, the other surface glycoprotein of influenza. That's a very important antigen, and it's a D463N and an N465S. This creates a potential N link-like constellation motif, so it adds a sugar moiety to the outside of that

glycoprotein. And that can really dramatically impact antigenicity. Viruses with HA genes belonging to the 2a1b subclade 2B with all these changes or the 3C clade were not detected in this period. So we saw some reduction in diversity.

The summary of A(H3N2) viruses continued is that the ferret antisera raised against cell culture propagated Hong Kong/45 recognized the 3C.2a1b.1a viruses well. The group within the subclade 2a also were recognized but a little bit less well than the 1a group. And the group within the 2a that had these substitutions at 159, these are some of these most recent viruses found in Bangladesh -- were recognized poorly, very poorly by the Hong Kong/45, the current vaccine. The ferret antisera against the egg propagated recognized all these viruses poorly.

Now, ferret antisera to cell culture propagated A/Cambodia/e0826360/2020 and A/Tasmania/503, which are in this 2a group, recognized viruses from the 1a and the 2a subclades well. And for viruses in subclade 2a that had these other additional

substitutions, it recognized those less well, but it still recognized those viruses in contrast to the current vaccine, which was very poor there. Neither group of 2a viruses was recognized well by antisera to the A/Cambodia/e0826360 in HI or VN assays, so there was some reductions there as we typically find with viruses from egg isolates.

Final bit for the H3N2 is that the human serology studies with serum panels from people vaccinated with Hong Kong/2671-like or Hong Kong/45-like viruses, which are in this 1b group, the post-vaccination GMTs were significantly reduced against cell culture propagated subclade 1b or 2a viruses but not against the 1a or 2b subclades or the 3a subclade. That's that cross-protection that I was illustrating that's elicited with 3a in particular. When compared to titers against egg propagated Hong Kong/2671 reference viruses, I didn't show you this data, but significant GMTs are observed against all the cell culture propagated viruses. And this is a typical effect, so it's not very useful for looking at what's

antigenically distinct to humans when we use that analysis. For antiviral susceptibility, we really didn't see viruses out of 140 that showed any reductions to the neuraminidase inhibitors -- so that's always good news -- or out of 147 to the baloxavir prolinase inhibitor. All right.

I'm going to turn our attention now to the influenza B viruses. So you've gone through the hard part. The H3s are always complicated to follow. Hopefully, it wasn't too bad. Here's the distribution of B virus activity geographically over the globe from September 2020 to January 2021. Again, light activity for most regions, but we did see some strong B activity in parts of Western Africa, for example -- stronger, anyway.

So the influenza B viruses, again, this graph looks similar to all of them, which is an unusual year. I won't spend too much time on that. Remember, B viruses have two lineages called the B/Yamagata and B/Victoria lineage, and they are depicted here as to their percentage. And it's pretty easy to see in this

donut shape that 99 percent of the viruses where lineage was determined were B/Victoria. We've seen very little B/Yamagata.

And so I'll spend the time on the B/Victoria as I mentioned in the outline. Some of my slides really aren't showing up well today. If that one -- that was the phylogenic analysis. This is showing the clade distribution, and so basically all the viruses circulating are in this one clade, V1A.3, which is pretty good news.

And I'm glad this slide shows up. So this is a little smaller view of the phylogenic analysis. The one that didn't work is a very large file, so that's probably why. But the main thing I wanted to point out again is the evolution of the virus in this tree is really moving from the bottom to the top for the most part. And we had a lot of the viruses in this V1A.3, the main V1A.3 clade, which runs from down here to up here -- all these viruses circulating -- are really B/Washington/2-like. That's the vaccine strain recommended for cell and egg.

So you can see where they all sit. This boxed area is this small group of virus that originally emerged in 2019 that has this N150K, G184E, and then N197D, which results in the loss of a glycosylation site. And this is further evolved and split into two groups, this 220 kind of group, which really circulated in China for the most part, and another group with P144L, which was more limited but had more geographic distribution.

And this is showing the reactivity of ferret antisera recommended for the vaccines this last season, so B/Washington cell like and egg-like. Again, the patterns for the totals are pretty similar, and the top part is showing February 2020 to January 2021. We had a lot more viruses to analyze.

And then the bottom part is showing just this most recent period from 2020 to 2021. So you can see about 70 percent of the viruses were well recognized in the early part of the year, and where they were low was primarily CNIC or China, the China National Influenza Center, showing the biggest reduction there. And then

where the viruses were seen in this period were primarily in China, and so they were pretty much the similar viruses. And a lot of those are considered low to this Washington/2 candidate in their hands. We see a pretty similar pattern, which is always good news, with the egg antigen.

Again, I'll show you some cartograph. You guys are probably all experts at this by now, but you can see the gray dots are where viruses existed that are older than 12 months. And here, we're looking at data from our collaborating center in Atlanta where the more recent viruses -- we did have a few that were double deletion or could be characterized in the last 12 months but not in the most recent period. Here's where the Washington/2 cell virus sits and all the viruses really circulating recently around that. The very old virus is Brisbane/60. That was two vaccines ago, and this Colorado was the last vaccine prior to the Washington.

Now, on the righthand side I've broken out this small 150K group in these colors of green so that

you can see them more easily. Again, here's where our B/Washington egg sits, and these start to get outside the sphere of antisera recognition. So this is starting to become an antigenically distinct group. And then you can see how well this B/Washington cell sits right in the middle of most of the viruses that were tested, and that's what we want to see.

This is a different way of looking at cartography. Here, we're doing cartography of the sera and not of the virus. And so you haven't seen this before, but I thought it would be helpful. What you do is the sera is dead set in the middle of this particular one on the left-hand side using sera against B/Victoria/705. This is a B/Washington/2-like virus. And you can see the sera's reactivity profile determined as to how well it would cover within four-fold of the homogenous titer, so we consider that good coverage when we see something like that. And so some of these 150K viruses, while they are showing antigenic distinction, do show some cross protection with this sera.

Now, if we make sera to 150K virus, it actually sits up in this corner. I can't really show it, but it's right about there. It will cover these viruses pretty well, these 150K viruses, but it won't cover all the other viruses that are circulating.

So this is another way to do the analysis is to take the sera and ask the question "What will it cross-neutralize?" So it's not just about getting the best match. It's about getting sera that does neutralize the viruses that are all co-circulating at the same time or predicted to co-circulate in the future well.

And another piece of the puzzle is always the human serology. How well does the vaccine induce antisera that protects against the new emerging clades? And so it's the same serum panel we've described on this side, and now we're doing geometric mean titers against B/Washington/2 cell, which is in this V1A.3 group. And then we always, as I pointed out before, select viruses that are different. So these are the viruses that are the same in the first two columns, but

then this one, Maryland/24, has an additional substitution that could impact antigenicity. This is the group that had the 150K change that I just pointed out with the ferret antisera showed some differences but also showed cross-reactivity with the Washington/2 cell antisera.

This is another subclade that we have our eye on from Lebanon, the 2016 viruses. And it has an important constellation change at 233 and yet another one from Florida and then an older virus clad, the V1A.1 -- this is Iowa/6. This is a double deletion virus that was a previous vaccine candidate.

And I walked through all that sera to illustrate we're testing a lot of different things. What you can see is a lot of green, and that is good. Green is good. And that's true even for this virus group that's considered a bit antigenically distinct and was expanding in China.

And I won't belabor the bubble plot, but you can see the same thing here. Looking, for example, in the pediatric three- to eight-year-olds you can compare

Flucelvax and the egg vaccinated individuals. Pretty similar responses against the Washington/2 egg or the Washington/2 cell, which you can see there. For example, here good increases, and sometimes you get better increases in titer with the egg antigens.

And then you can also see here that there's a lot of protection induced against these viruses. This is in the Rhode Island column here with the 150K group by this vaccine, even in this younger population. So that's important.

So to summarize the B/Victoria viruses, they've greatly predominated over the Yamagata lineage. The majority of the viruses from this time period were identified in China, so that's from September to January. The HA phylogenetics -- all the HA genes belong to this major subclade, V1A.3. These have deletions for the residues 162 to 164, which was their major antigenic change and why they expanded so rapidly in the past. So they were antigenically distinct group of virus. Many of these also share this G133R substitution.

So a smaller subclade in this group was this 1A.3 viruses that have the 150K substitution along with these other changes. Now, that group was very small last year and did start to expand. And that's what we saw in China, primarily viruses like that. And this is already separating into two other subgroups, one of those that on the phylogenetic tree have this V220M and P241Q, which was in China and West Africa. And another subgroup has the A127T, P144L, and K203R. They were found in Europe, West Africa, and Oman.

For their antigenic characteristics, most of the viruses tested since February 2020 were recognized well by ferret antisera raised against the cell propagated or the egg propagated B/Washington/2/2019 virus. For the 1A.3-150K subgroup that predominated since September, they did show reduced inhibition by ferret antisera raised against the B/Washington viruses. However, ferret antisera raised against this group of virus, while it well inhibited themselves -- you know, it well inhibited homologous viruses with the 150K, they poorly inhibited most of the other viruses

with 1A.3 HA genes.

For post vaccination human sera, generally well inhibited all the viruses, including the 150K subgroup, and antiviral susceptibility, again, really in good shape. 144 viruses were analyzed. All were susceptible to oseltamivir. One showed some reduction to the zanamivir. And with the 16 viruses that were tested for laninamivir and peramivir, all were permissive or susceptible. And then, there were no viruses analyzed that showed reduced susceptibility to the baloxavir either, which is the polymerase inhibitor.

So I'll turn your attention to B/Yamagata, and as I promised, we should have some time for questions and answers. This will be pretty brief. Again, that tree's not showing up, but this is a large phylogenetic tree showing all these viruses circulating are very similar to each other. In this period, we didn't have any Yamagata viruses with collection dates after August 2020. We at CDC were able to get some Yamagata viruses over December from international sources, as well as

late in our season last year, but not in this period. A few viruses with collection dates in earlier 2020 were available, and that's what I just mentioned.

This is showing you antigenic cartography. Again, old viruses are in gray. The most recent that we could test are in red, and they're still showing nice proximity to the B/Phuket cell and egg antigens.

And so to summarize those, the Yamagata lineage were rarely detected. We had no viruses available with collection dates after August. All the viruses from 2020 had HA genes in clade 3, which is where B/Phuket/3073 is, so it shares that with the vaccine virus. Most recent viruses were well recognized by ferret antisera cell culture propagated and egg propagated B/Phuket/3073, and post-vaccination human sera well recognized viruses representative of those most recently circulating. And I didn't show you that because it's a bit boring.

So we really have to acknowledge everybody this year, more so than ever. I mean, we always put these slides up, but our WHO collaborating centers and

colleagues in all those collaborating centers really did a bang-up job. The Geneva staff, the central regulatory labs, and really who we're wanting to thank most are the U.S. and international partners, so the GISRS. They really beat the bushes to get viruses, and so I think this may address some of the questions we had earlier on are they just not being noticed or detected.

Well, people really looked. The CDC developed a multiplex real-time PCR assay that detects both SARS-coronavirus and influenza A or influenza B, as well as a housekeeping gene in the single assay. And we distributed that. After it was distributed to all our national public health laboratories here, once we had enough kits around, we distributed that to the National Influenza Centers globally. So they could simultaneously check subsets of their viruses for both influenza and SARS. For example, if it was SARS negative and they were using a SARS only test, they could repeat it with that, or they could just use that flu multiplex to start with. And that was done at all

the state public health laboratories in the U.S. as well.

And so fitness forecasting, we had a number of partners there. I didn't show you much of their data this year. It's harder for them to fitness forecast when there's not that much virus. And a special thanks to Becky Kondor, Min Levine, Larisa Gubareva, and John Steel who all contributed significantly to everything I showed you. These are team leads in my branch. Becky is also the deputy director of the WHO collaborating center and does a large part to put all our data packages together. And with that, I will just leave you with some information showing. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Wentworth, for summarizing a very complicated dataset in very clear terms. I will invite now my members -- my colleagues to raise the hand function if you have questions to Dr. Wentworth. I will begin by asking about the H1N1. We are moving from the 5A1 to the 5A2 in terms of recommendation for inclusion. Maybe I did not quite grasp it, but is there a preponderance that

we observed the epidemiology in A2 versus A1? And is the geographic distribution sort of spreading? Because maybe I'm misreading, but it seems like this year compared to many other years there was more compartmentalization of where the viruses occurred. The color figures used to blend a little more.

DR. DAVID WENTWORTH: Yeah. Well, I think you picked up on all of that very well, so I don't think you misinterpreted anything. And it's a very -- it's one of those difficult situations. So I think our discussions earlier about reduced travel, we really did see more compartmentalization of different clades of flu virus and even of the evolution -- you know, branching evolution from what used to be one virus -- like I showed you Bangladesh was doing one thing, Cambodia doing another in the H3s. And so that makes it challenging.

For the H1N1s, we really saw a paucity of those viruses all around the globe. There just wasn't a lot. And so to say that the clade -- the earlier clade, the A1 versus the A2 -- so the A1's the 187

group and the A2's the 156 group. Those two clades were not equal. There was probably about 70 percent of the older virus and only 30 percent of the one that's being recommended.

However, if you remember from the Southern Hemisphere, what we saw was the emergence of that clade and the rapid displacement of that clade -- of other clades by that virus in the one season so that at least 50 percent of the viruses that circulated in the United States the year before. And that partly drove the change for the recommendation for the Southern Hemisphere 2021.

The other things that drove that change and drive the recommendation here are human serology, which shows really great risk from that antigenic group and very little risk from the A1, which everyone's been vaccinated with in the United States, for example, about 180 million people, and have had prior infection or exposures to. So we saw that great kind of reduction in geometric mean titers when you look at those A2 156K viruses, so that's important.

And the thing I didn't show you but we did have in the Southern Hemisphere was we actually were able to see in the United States and in, I think, Canada they saw this as well in two different epidemiologic studies clade specific vaccine effectiveness reductions for the 156K group viruses. So I know probably -- I'm glad you asked the question. I was thinking of trying to put that in, but it's very old data. And it's published, but that also -- it's one of the times where we had enough viruses from both clades cocirculating in a season to do that effectively with good statistical relevance. So it's the human serology and the clade specific VE that really says the 156K group has a great risk. You can never predict what flu will do, but we do understand that one has a greater risk than the 187A group of viruses.

DR. HANA EL SAHLY: Thank you. Dr. Paul Spearman, please put your camera on and ask your question. The mic.

DR. PAUL SPEARMAN: Thank you very much. Again, that's tremendous amount of data. I also had a

question related to Hana's about the choice in H1N1. So when you have two different clades and one it sounds like is more emerging -- and that's what we've chosen. But it sounds also like sera raised against that clade 5A2 doesn't really cross protect against the 5A1. So there's kind of a danger there and is it just -- in some of your other clade selections for the other strains, it seemed like you could find one that really could cross protect against multiple clades. And is that not possible with H1N1 where, you know, there's certainly going to be naïve kids that aren't going to have seen the prior vaccines will be very susceptible? But maybe it won't circulate. Is that part of the thinking because of all the protection in the community?

DR. DAVID WENTWORTH: Yeah. So fantastic question. So I'll try to -- I take it I probably wasn't as clear as I could be. So when we take ferret antisera, ferret antisera is very focused immune response. It has very immunodominant focused immune response. And with H1N1 viruses in particular, it can

be very focused on this SA site where the 156K substitution is. So it's very easy to show that they're antigenically distinct from each other, the 187 virus -- so the 5A1 and the 5A2. They're antigenically very different from each other.

But remember, that's in a naïve animal. And in a human, we get broader response even in a naïve person usually, so you get some more cross protection. The thing is both of these -- the main difference between both of those viruses is at this 187 position versus the 156 position. But they share many other changes along the way; right? So they share all the 5A changes, which are basically almost all the viruses -- which is all the viruses circulating. Right?

So there's a certain level of comfort, and even if it's an antigenically advanced virus and it isn't the one that predominates that you are going to induce immunity. And it does show some cross protection. I tried to show you that with some of the bubble plots. Obviously, we can't show that in humans until people have been vaccinated with it.

The only thing I can mention that's kind of related to that, you may remember that we had the delayed decision for the H3 viruses. We chose that Kansas/14 because it was kind of like this 156K group. It came up late in the season. It came up very rapidly. We didn't have a vaccine candidate for it yet. We had some in the works, and we didn't have enough data to say if it's going to continue to expand and whether or not the antigens would produce a good immune response.

We also see very distinguished in ferrets antigenic profiles between those two. But when we take the serum from people vaccinated with Kansas, it induced great cross protection against these other clades in all the groups with the exception of those young pediatrics, the six month to 35-month-old. That's where you see the biggest, you know, lack of prior immune response that would be induced as a memory response.

And so that's what I can tell you about that. So I think it's really what I was telling you about the

risks of that 156K virus group being greater than the risk to the other group, which has basically circulated for a while in all of us and has been in our vaccines.

DR. PAUL SPEARMAN: Great. Thanks. It sounds like, if we're not a ferret, we'll still get some cross protection.

DR. DAVID WENTWORTH: We're also one (audio skip), you know.

DR. HANA EL SAHLY: Dr. Michael Kurilla.

DR. MICHAEL KURILLA: Thank you. David, I had two specific questions. One is when you look at human antisera, it looks like you're largely taking that from individuals who were vaccinated in the previous year, and I'm wondering if you've ever looked at individuals who had a natural flu infection the previous year to compare that to what the vaccinated ones looked like and if there's any sort of qualitative difference. The second question is you present a very detailed, deliberate analysis. I'm wondering is there any type of hypothesis testing to actually determine whether in fact the analysis you're doing is actually improving

over time in terms of the effectiveness of the vaccines?

Are you getting it right more often and leading to a reduction in mortality and morbidity from flu? I recognize there's a lot of moving parts here, but I'm just wondering are we getting better at what we're doing? Or are we just doing the same thing every year because we think it's as good as we can get?

DR. DAVID WENTWORTH: Yeah. Thank you for those questions. The second one's very hard to answer. We haven't done like a hypothesis type of analysis to illustrate whether or not some of the new -- we really haven't changed so much as added more. We tend to add more as to whether or not the new things we're doing improved. And I think we need longer term analysis to understand that. Like the fitness forecasting plays a role in trying to understand, you know, better what viruses will circulate in the future, and that's aided by a lot more next generation sequencing around the world that gives you more data.

So the short answer is I think we're getting

better, but we haven't done an analysis for that. And I think that's something we can look into more. And I also think, no matter what, we can have a poor VE, and it may not be totally related to the vaccine selection.

Again, you can look at these slides later, but what you can see is sometimes people don't respond as well to the vaccine. And we don't understand why that is. Like, why doesn't person A respond as strongly as person B to the same vaccine? That may get to the first part of your question, which was have they all been vaccinated previously, or have they been naturally infected previously?

And unfortunately, we have very limited data as to what's happened with these folks before. We ask for people that haven't been vaccinated previously for the most part because we want to get a more naïve response, but it's in part how people fill out a form and survey prior to being -- entering the study and having their blood drawn. We can see sometimes in the pre -- if you look at their pre-sera, this has to be a very detailed analysis when you do this. But if you

look at their pre-sera, you can sometimes see that they have a high titer to the vaccine antigen and maybe a lower titer to something that was circulating around the same time that was similar.

But that becomes very hard to tease out. It could just be that they were infected by something very much like the vaccine. So I can -- because that was -- I don't know if that addressed your question or not. I can open for follow up if you want.

DR. HANA EL SAHLY: Thank you. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you and thank you for that detailed overview. I'm putting on my allergist hat now because I take care of patients who have egg allergy, and I wanted to know why are some of these vaccines egg-based and others recombinant. What determines which lineages are recombinant and which are egg-based, and is one type more effective than the other? And does there really have to be one of each type?

DR. DAVID WENTWORTH: Wow. Great questions. So the first flu vaccines were all egg-based, so we

didn't have recombinant and cell-based vaccines in the beginning. They were all egg-based, and this is in part because it was -- one of the reasons the influenza virus was able to be isolated was because it grew in eggs before we even had tissue culture capabilities in the laboratories. So in the 1930s, they could isolate influenza using embryonated hens' eggs.

And in the past, the isolation in eggs was very easy. The virus didn't change very much, and it grew very well in egg. And that's continued for the most part with many of the viruses. The exception is the H3 viruses, which have become so adapted to humans since their introduction in 1968.

So originally, they were from avian, so the HA was from an avian source. It jumped into humans, caused the pandemic in 1968, and then ever since then it's been evolving more and more to the human receptors and binding more poorly to the avian receptors. And so the H1N1 virus is a relatively recent virus from pigs, which share a lot of the same type of receptors as avian. So it doesn't have to undergo as many changes,

so that's kind of a long virological story about what happens with the virus when we put it in eggs. Some have to change a lot, and some don't have to change as much in order to replicate efficiently.

Eggs also are globally the most important vaccine substrate in the world because that's what most people can produce at high quantities to get to a half a billion doses of vaccine. In the U.S., we have started developing newer technologies, like the cell-based recombinant cell-based vaccines, which are -- certain companies can do. And they have license through the FDA, and they produce a subset of the vaccines used for the United States. But I don't have the numbers in front of me, but I would say about 150 million doses are produced in eggs. And then the rest of that 40 million comes from cell-based candidates and recombinant candidates.

Recombinant is also a pretty new technology for flu vaccines, and it's being used more and more. And so we're trying to accumulate that data to understand is one better than the other and why. And

it might seem on the surface when you look at the ferret sera that it would be obvious, but I think when Dr. Weir or other colleagues at the FDA can look at this in a different way, they're looking at how well it induces a strong response and how that cross protects against many viruses and what the VE is. So I think -- when I say VE, I mean vaccine effectiveness studies.

So I think down the road there'll be enough people vaccinated with the different platforms that you can do platform specific vaccine effectiveness studies. And that looks at the whole population, all of us with all our different genetics, the different viruses. So it takes into account so many things.

DR. JAY PORTNOY: So should we expect to see more recombinant viruses over time?

DR. DAVID WENTWORTH: Yeah. It's really -- I think the market will drive that, right? So I think the recombinant cell-based are new technologies that to me represent a good advance in flu vaccine technology.

DR. JAY PORTNOY: Thank you.

DR. HANA EL SAHLY: Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you very much. That was really great, and obviously this is the really important data that is the basis for our decision today. So really understanding this is really helpful, so thank you for your explanation.

My question was related to a previous question in that trying to understand how sort of good we are at predicting and how we are using the data that we want. Moving towards not having to analyze the difference in these viruses as you've very beautifully outlined, how do you -- and there's a lot of work now going towards having a universal vaccine, really trying to figure out what part of the virus is actually universal so that we could potentially have immune response to it and not have to do this every year. When you do your antigenic sort of analysis, are you also looking at areas that actually may be overlapped so that this kind of information could be used as we move forward instead of looking at really how they differ?

DR. DAVID WENTWORTH: Yeah. That's a really interesting point, and of course there's a lot of work

funded by our federal government towards universal flu vaccine in the hopes that we could get a shot once every five years, once every 20 years, those kinds of things. We don't focus on those epitopes that would be more universal flu vaccine epitopes, and I'll explain why. Because those epitopes don't change. They don't really help us with the current flu vaccine. Basically, we get a similar answer across those epitopes from the different antigens because those are shared across all those antigens.

Many of the changes that I -- so, for example, we'll take a certain type of universal flu vaccine would be one that's focused on the stem of the hemagglutinin rather than the head of the hemagglutinin. Where influenza mutates is really primarily in the head of the hemagglutinin, and those are the ones that evade neutralizing antibodies. Some antibodies that react with other parts of the hemagglutinin are not neutralizing, so they become very difficult to measure, for example. You have to have different types of tests set up to understand how well

you're inducing the, quote/unquote, universal epitopes.

And we have -- for the humans, we have quite -- for human sera, that would be extremely challenging. For ferrets, you could do it. You have to have -- how it's done is you make chimeric hemagglutinin molecules that, say, for example, have a different head completely that can't be recognized from an H5 virus that circulates in chickens or whatever or an H6 virus that circulates in chickens. And then you put the stem of an H1 virus, so you have to make these by reverse genetics and recombinant virus technologies. And then you can use that virus to see how well it's neutralized by the various sera.

And what I'm saying is if I were to do that with a ferret sera that we create, they would all be about equally neutralized because nothing changed on that part where the antibodies are going against. It's quite a different thing. I think part of universal is stimulating high levels of antibodies to those conserved epitopes rather than low levels and have then be high affinity rather than low affinity. So we're so

busy doing the kind of analysis to make the flu vaccine recommendations that that universal vaccine's bases really in extramural programs from NIH and investigators around the world doing more pre-clinical work.

DR. HAYLEY GANS: Thank you so much. I look forward to the day that we can get our vaccine every five years.

DR. HANA EL SAHLY: I will stay on the question of H5. You mentioned it with regards to the universal flu, but is the H5N8 still localized at the outbreak level in Russia? Do we need to worry there?

DR. DAVID WENTWORTH: That's not a typical VRBPAC question. So yeah, there has been a small outbreak of H5N8 viruses that has been zoonotically transmitted to humans in Russia, and we're working to understand better about that virus. I think there was about eight infections. We're still trying to narrow down data or our colleagues at Vektor in Russia who are part of the vaccine consultation meeting and have provided some data and are following up on and trying

to get serum to understand if people were really infected or if they just test positive because they were around poultry that had very high levels of those virus. And you can swab them, and they were positive.

So there's a lot of things to still be worked out. Usually during the vaccine recommendation meeting when we have it in person in Geneva, we cover the zoonotic viruses at the same time. However, the zoonotic virus for selecting vaccines for pandemic preparedness is what we do there. And I never present that at VRBPAC, but what's done in that setting is to go through the very giant iceberg of viruses that are circulating in the animal reservoir trying to understand which ones have been zoonotic, which ones have zoonotic potential, which ones have pandemic potential.

And then every six months new pre-pandemic candidate vaccine viruses are selected from these groups for production in good laboratory practice to create seed stocks so that it can then be used in the event of a pandemic, and they're available to all the

manufacturers. So manufacturers can acquire those seed stocks and just make technical lots and see how they grow and do -- there's also clinical studies done from them. And so that's kind of a long-winded answer to the Russian question, but it turns out we already had selected a vaccine virus for this group last VCM, so in September. And that one is in production or nearly completed. The CNIC, the Chinese National Influenza Center, collaborators -- WHO collaboration are at Chinese National Influenza Center developed that resource.

So it does exist. So it's in a high growth background, and it does exist. And they'll be testing sera against that virus to see how well it cross reacts against these H5N8s from a pandemic preparedness perspective.

I mean, we have seen H5N8 jump into -- H5 viruses of many N subtypes, primarily H5N1, zoonotically transmitted to people many times in the past, and most of the time these are very localized outbreaks without evidence of person-to-person

transmission. And so we are definitely watching this situation as we do every zoonotic event, and the first thing that happens is we try to look for if it's acquired the ability to transmit among humans. And we also simultaneously look to see if we already have a vaccine candidate that's made. And if we don't, we start making one.

DR. HANA EL SAHLY: All right. Well, thank you so much for this presentation and for taking all these questions. At the moment, we will have a ten-minute break in our agenda, and it's 10:20 my time or 11:20 Eastern Time. We will reconvene at 11:30.

[BREAK]

MR. MICHAEL KAWCYNSKI: Hi. And welcome back to our 165th VRBPAC Meeting. We now are coming back from break, and we are entering into our middle portion of the agenda. I'd like to hand it back Dr. El Sahly. Dr. El Sahly, take us away.

DOD VACCINE EFFECTIVENESS REPORT

DR. HANA EL SAHLY: Thank you. It's my pleasure now to introduce Dr. Kevin Taylor, the Global Emerging Infections Surveillance Branch, Armed Forces Health Surveillance Division, Public Health Division, and Dr. Kathleen Creppage also from the Armed Forces Health Surveillance Division. They will give us an overview of the Department of Defense vaccine effectiveness report. Dr. Taylor.

LTC KEVIN TAYLOR: Hi, good morning. As was already said, my name is Lieutenant Colonel Kevin Taylor. I'm with --

MR. MICHAEL KAWCYNSKI: Dr. Taylor, you had your camera on. Can you turn it back on again?

LTC KEVIN TAYLOR: I think I lost connection altogether. I got to request re-entry into the --

MR. MICHAEL KAWCYNSKI: That's okay. Here you go. We got you.

LTC KEVIN TAYLOR: Okay.

MR. MICHAEL KAWCYNSKI: Just give us a second

and we'll make you back to a presenter. You should be able to go ahead and turn your camera on again. And trying to find you on the list. Where'd you go? Let's move him up to a presenter.

MS. KATHLEEN HAYES: He's under presenter already, so he's okay.

MR. MICHAEL KAWCYNSKI: Okay. There you go. Are you able to move your slides, Dr. Taylor?

LTC KEVIN TAYLOR: Yep.

MR. MICHAEL KAWCYNSKI: There you go. Perfect. Take it away.

LTC KEVIN TAYLOR: All right. Thanks again, yes. I'm Lieutenant Colonel Kevin Taylor. I'm with the Defense Health Agency's Armed Forces Health Surveillance Division. And I'll be presenting the results from the DoD Global Respiratory Pathogen Surveillance Program and those partners that contribute to this very important effort each year. We don't have a whole lot of data to present on today, but hopefully it'll be a little bit of a useful add-on to the great presentations you already heard this morning.

I'm also filling in for the very capable Commander Mark Sheckelhoff who led this effort within our division over the past few years but who departed recently for his next public health service officer assignment. I'm also joined by Dr. Kathleen Creppage who is the portfolio manager for the respiratory infections focus area here within our office and who is truly instrumental in pulling together much of what we'll be presenting here today.

So today I'll be presenting data on the 2020 to '21 influenza season from our influenza surveillance network, including an overview of the past three years of surveillance data with a snapshot of what's taken place, of course, during the past few months during the pandemic. Included here will be surveillance data from our partners in North America, South America, Europe, and Middle East, Africa, and Asia. So I know it was mentioned on the agenda that I'll be doing a talk on vaccine effectiveness, but we're actually going to be covering just a general surveillance for flu as well.

As with the other contributors, our analyses

this year are going to be very limited in comparison to previous years due to the low number of influenza cases captured through our surveillance program over the past several months. And with that said, I'll be presenting a brief summary, still, of the phylogenetic analyses developed by the U.S. Air Force School of Aerospace Medicine or what I'll refer to as USAFSAM. And this may, of course, look different compared to previous years. For this season, we only had 12 influenza samples received by USAFSAM for sequencing, so obviously a much more scaled down analysis.

In addition, I'll be presenting a mid-year estimate of vaccine effectiveness developed by the Armed Forces Health Surveillance Division at the Analysis Branch. We won't be sharing data on antigenic characterization for this season like we have in the past. That data is usually provided by the Naval Medical Research Center, and that's just because of insufficient data this time around.

All right. So I'll start off today with a brief overview of the influenza surveillance within

DoD. Flu surveillance is included as part of the DoD Global Respiratory Pathogen Surveillance Program that I mentioned before, which is managed out of the Global Emerging Infections Surveillance Branch here at AFHSD. The GEIS Branch is a DoD asset dedicated to the surveillance of infectious diseases primarily but not exclusively in the military community.

Our flu surveillance program extends over 400 locations in over 30 countries, utilizing the network of DoD laboratories that are across the globe. In addition to monitoring U.S. military personnel, our partners have relationships with foreign governments including ministries of health and ministries of defense and academic institutions which provide disease surveillance on local, national populations as well. Our laboratories have pretty extensive characterization and capabilities including cell culture, PCR, and sequencing capabilities. On average we have about 30,000 or more respiratory samples collected a year and analyzed within our surveillance network. We also have access to extensive health records for the active-duty

military population, which are typically an important source of data for monitoring influenza activity within the DoD and conducting vaccine safety and effectiveness studies.

I'd like to briefly show where our GEIS-Supported Influenza Surveillance is active. The GEIS network is spread across six of what we call geographic event commands shown here. And multiple laboratories conduct flu surveillance routinely as a part of this program. One of the core GEIS laboratories, USAFSAM, which I mentioned before, has a particularly wide geographic footprint and surveils for flu across many sentinel sites in the U.S., in Europe, and also locations in the Indo Pacific region. However, testing for flu obviously declined significantly in 2020 and into 2021 in the midst of the pandemic. And you'll see that borne out in our data we present here today.

In the next several slides I'll present data on influenza subtypes detected by several of our GEIS network laboratories but reiterate again that flu surveillance has been impacted significantly at these

sites -- restrictions and lockdowns that resulted in reagent shortages, shipping delays, staffing reductions that have really impaired normal surveillance activities. And I have a few examples here what's been going on. And then, of course, this has been taking in place in an environment where resources are being shifted to COVID surveillance and where flu rates are just already diminished at least in some part by the public health measures implemented in response to the COVID pandemic. So you'll see this impact in the coming slides as I present data by region. And in fact, I'll move through these slides pretty quickly since there's actually not a whole lot of data to present for the current (audio skip).

All right. On the following subtype calculation -- I'm sorry -- circulation charts, the MMWR week is along the X axis and the percentage of positive samples is along the secondary Y axis on the righthand side. Number of specimens is located along the primary Y axis on the left-hand side. We have three years of data shown here starting way back in the

week 40 of 2018 on the left-hand side going to the most recent data for 2021 on the righthand side. Different color of bars, of course, indicating different influenza types and subtypes.

This particular graph represents surveillance data for military members including recruits and other military dependents residing within the United States and also some select civilian populations along the U.S.-Mexico border. Influenza A, subtype H1N1 has been the dominant subtype in the previous season. And low levels of Influenza B were also evident. However, Influenza B has pretty much been nonexistent this season with our surveillance, and there has been no cases detected in these populations in recent (audio skip).

Okay. Here we show data from South America, and this comes from U.S. and civilians as well as the local military and civilian populations in Peru, Panama and Columbia and Honduras. Respiratory data is primarily limited to populations, though, in Peru and Panama for the latter part of 2020 and early 2021. The

predominant subtype at the end of the previous season was Influenza B for us with lesser circulation of H1N1 and H3N2, but there have been no flu cases detected for the current season in this region.

This graph represents surveillance data for military members and their dependents in nine countries in Europe including some in Kosovo and Romania. And this is actually the first time that the GEIS network, at least, has had samples from these Eastern European countries. This season's flu activity, like other regions, is low. Few positives were detected for H1N1 and H3N2. And, of course, the European Centre for Disease Prevention and Control notes a kind of similar decline in positivity as of week 30 -- I'm sorry -- week 53 in 2020. Although, what they do show is kind of an equal distribution across -- of 50 percent A and 50 percent B among the 100 or so samples that they have.

This data here represents U.S. military personnel and civilians as well as a handful of local and national populations within the large number of

Asian countries in which we operate, including Bhutan and Cambodia, Nepal, the Philippines, and Thailand. And then more recently, we added Mongolia to this list in early 2021. Surveillance in Asia showed dominance of Influenza A (H3N2) almost exclusively, although there has been no influenza detected over the past several weeks through our surveillance. And this is despite the fact that testing remained fairly steady throughout most of the pandemic in this region for us.

This shows data for U.S. military and civilians in select locations within eight countries in the Middle East. In the Middle East, we had flu activity declining at this time last year for us, but there's been almost no positives detected in the past several weeks with the exception of a few Influenza B detections in the past couple months.

All right. Surveillance in East Africa comes from primarily foreign military and civilian populations in Kenya, Tanzania, and also Uganda. There are some gaps in the data due to logistical issues during the pandemic. But positivity rates were still

low even when testing was consistent coming from these sites. Influenza circulated at low levels in 2020 and 2021 in general, with Influenza A predominating in 2020. In the past few weeks, Influenza B has been detected in the region alongside Influenza A, subtype H3N2.

And then, our final region to go over, here we show surveillance data coming from military and civilian populations in Ghana. When aligned with the WHO Global Influenza Surveillance and Response System data, that they're almost identical. Influenza A (H3N2) and Influenza B were predominant in the current flu season similar to the 2019-2020 flu season but markedly lower compared to the prior year.

Okay. All right. So in summary, our flu surveillance data from our global lab partners is very limited for this flu season. Our surveillance in North America, South America, Europe, and Middle East detected almost no cases, with a small amount of Flu A activity in Europe and Flu B in the Middle East. Surveillance in Asia showed H3N2 circulating at low

levels in weeks 29 to 42 but with nothing detected after week 52 our network. Surveillance in East Africa showed some low-level A activity with some Influenza B activity beginning after week five. And our surveillance activities in West Africa showed both H3N2 and Influenza B activity but at very low levels compared to previous (audio skip).

All right. So next, I'll present the phylogenetic analysis completed this year by our partners at the U.S. Air Force School of Aerospace Medicine, USAFSAM. And while in previous years our partners at USAFSAM were able to acquire well over 1,000 samples for sequencing, this year's low influenza rates really resulted in much less to work with for a phylogenetic analysis. As I mentioned earlier, we only had 12 samples to be sequenced this year and available for analysis. All of these were H3N2 sequences from Southeast Asia. And I'll note that September 2020 samples were included in this analysis in order to capture as many relevant samples as we possibly could.

All 12 were in the clade 3C.2a1b. 11 of the

12 collected in September/November or December 2020 in Cambodia and Thailand were in the T131K amino acid substitution group with the additional substitutions of K83E, Y94N, I522M, G186S, F193S, and Y195F substitutions noted, placing them in the 2A subclade that, of course, Dr. Wentworth mentioned a lot earlier. The remaining sequence collected from the Philippines in December 2020 was in the T135K amino acid substitution group with the additional substitutions A138S and F193S placing it in the 1A subclade. The WHO H3N2 strain recommendation for the 2021-2022 Northern Hemisphere vaccine, which is in the 2A subclade, does a good job of recognizing both the 1A and 2A viruses identified by USAFSAM and represented here.

All right. Looking at the results by month, the Influenza A (H3N2) T131K subgroup was predominant at the start of the 2019-2020 season, and then the T135K subgroup became predominant in the last half of that season. However, the T131K subgroup kind of reemerged and circulated at higher proportions through the summer of 2020 and start of the 2020-2021 season.

Among our data for the current season, the 1A, or what you could call the T135K-A, and then the 2A, or the 131K-A, are the only ones detected for the T135K and T131K subgroups, respectively.

All right. So in summary, we've got very low flu rates thus far for the current flu season which left us with very little to work with just with those 12 sample sequences and sequence in all from our partners in the Indo Pacific region. All of these resided in the, as I said, the 3C.2a1b clade with 11 falling in the 2A subclade and one in the 1A subclade. Of note, the WHO strain recommendations for the 2021-22 Northern Hemisphere vaccine seems to inhibit viruses in both these subgroups.

And while we have no sequences this year for either H1N1 or Influenza B viruses, the clades identified by USAFSAM at the end of the 2019-20 season were consistent with this WHO recommendation for the Northern Hemisphere. And so taken all together, our sparse H3N2 phylogenetic data this year along with what was seen with H1N1 and Influenza B data from the end of

last season does align well with the WHO recommendation for the 2021-22 Northern Hemisphere vaccine as I already mentioned. And the details of that recommendation, of course, listed here, but I won't read those out in detail, of course, since we've already gone over that in previous presentations this morning.

All right. Now lastly, I'm going to move on to a discussion of a vaccine effectiveness estimates performed by our Armed Forces Health Surveillance Division Epi and Analysis Branch. To start off, I'll mention that what typically comprises our annual vaccine effectiveness analysis -- we usually actually have three partners that contribute to this effort. We have the Armed Forces Health Surveillance Division Air Force Satellite at USAFSAM that usually provide vaccine effectiveness analysis for our non-active duty populations or beneficiaries that are not active duty within the DoD. And the Naval Health Research Center usually provides a VE analysis for military trainees or what we would call the recruit population.

However, the small number of positive test results coming out of these populations this year meant that we didn't really have any kind of meaningful analysis to present for vaccine effectiveness in the populations. So I won't be presenting any of that today. However, the Armed Forces Health Surveillance Division Epi and Analysis Branch usually conducts our vaccine effectiveness analysis for our active-duty population more broadly. And fortunately we do have some data to present for that population, which I'll discuss here in the next few slides.

All right. So the study designed for this analysis was a case test negative control design on active component personnel from all the military services including those stationed both in the United States, or what we call CONUS, and those stationed in foreign locations, what we typically refer to as OCONUS. Cases were lab confirmed by positive rapid tests or also by RT-PCR or culture assays. Test negative controls were those that presented for care and tested negative for flu either by RT-PCR or culture

assay. Those that were negative, though, only by rapid test were excluded from the analysis.

I'll present both the crude vaccine effectiveness for both Influenza A and B along with results adjusted for sex, age, prior vaccination, and diagnosis. And due to the limited subtype data, I'll only be able to present overall and type specific vaccine effectiveness for this particular population.

All right. A little bit more on vaccine information and what we had for those subtypes just to make it clear. So inactivated influenza vaccine was the only vaccine type used in this particular study population. It's also important to note that our active-duty population is a well-vaccinated population. And flu vaccine is basically compulsory for all active-duty personnel.

So almost all of the study subjects had been vaccinated for flu in the prior five years. We had a total of 219 Influenza A and 171 Influenza B cases to include in the analysis. And nearly all our cases were identified via rapid diagnostics tests, which is why we

have nearly no subtype results to include (audio skip).

Our breakdown by age group of both cases and controls is shown here. The U.S. military population, as you are probably aware, are relatively young compared to the general U.S. population, which, of course, will limit the ability to generalize these results to the broader U.S. population.

Here's the results of the analysis showing overall vaccine effectiveness and then for both Influenza A and B. The large difference between the crude and adjusted effectiveness for Influenza A can largely be explained by the distribution of cases over time throughout the season. So a large portion of the Influenza A cases were detected early in the season, in fact, over 40 percent in just October alone. So that is an explanation for that significant difference there as we go to the adjusted vaccine effectiveness for Influenza A. Whereas the influenza and test negative controls for the Influenza B were more evenly distributed throughout the whole (audio skip.)

The adjusted vaccine effectiveness for A did

not reach statistical significance, so important to note that. And while the effectiveness estimates for Influenza B and any type of influenza were statistically significant, do note the wide confidence intervals on those estimates (audio skip) part to the low number of cases included (audio skip).

So in summary, the overall midseason vaccine effectiveness was 29 percent with this analysis. But do remember that this is in a relatively young active-duty military population. It was somewhat higher for Influenza B at 40 percent, indicating some moderate protection, notably lower, though, when we looked at Influenza A. Although this did actually not reach (audio skip). We, of course, look forward to next year when we can (audio skip). I think we will be able to include, of course, the non-active duty and basic trainee populations that weren't included in this (audio skip).

And there are a few limitations to note with this analysis, specifically having to do with our ability to generalize the results. With this case test

negative control design, all subjects included in the study were individuals actually presented for medical care. So it's not actually possible to maybe assess vaccine effectiveness, vaccine impact on those that were less severely affected by their infection. Also, since the active-duty military population is highly vaccinated, as I mentioned before, with nearly all required to get the flu vaccine each year, this could affect our estimates of vaccine effectiveness as the repeated past exposures to vaccine could possibly attenuate some future immune response to vaccination. As I already alluded to, generalizing these results to older, higher-risk populations may not be possible given the age and general health status of our active-duty military population.

So with that I'll just say thank you for your time. I will just, of course, highlight all the partners that contributed to this effort here within the Armed Forces Health Surveillance Division, our Air Force satellite, and then also the numerous partners at our overseas laboratories, so many in fact, that I do

have to show it using two slides -- and then also our partners in some of those partner nations that I mentioned earlier, of course, appreciate and value all the great, great work they contribute to this effort. So with that I'll entertain any questions that may be out there.

DR. HANA EL SAHLY: Thank you, Dr. Taylor. I think Dr. Creppage is going to help take some of the questions. Is that correct?

LTC KEVIN TAYLOR: Yeah. So if there's anything that I may not be familiar enough with to answer that she could perhaps answer, I may ask her to chime in. But, yeah, I'm happy to entertain anything you have.

DR. HANA EL SAHLY: All right. Great. It is my interpretation that from your presentation and Dr. Wentworth's presentation it seems that West Africa is sort of the outlier in terms of having more flu activity than others. Any potential explanation or that or (audio skip)?

LTC KEVIN TAYLOR: Yeah. I don't really have

a good explanation for that. Obviously, what we saw there was predominately H3N2. And I don't know if just the -- is it perhaps impacted by the COVID pandemic, just a set of public health measures that are different than what's being implemented in other parts of the world resulting in the flu transmission being a little bit more possible in those kind of locations. At the end of the day, we're still not detecting a whole lot of cases of flu.

And part of what you might see there is just the fact that flu rates for us in our surveillance is just so low in so many of our other regions that the small amount that we're seeing there really kind of just jumps off the screen. But I'll let -- I don't know if Dr. Wentworth is still on the line if he has anything to add, given that he kind of did highlight that in his presentation as well.

MR. MICHAEL KAWCYNSKI: David, Dr. Wentworth, let makes sure that you're unmuted. Make sure you unmute your own phone.

DR. DAVID WENTWORTH: Yeah. Yeah. Sorry

about that.

MR. MICHAEL KAWCYNSKI: No problem.

DR. DAVID WENTWORTH: Yeah. I think I don't have a great explanation for it either. So I think it was well presented. And we've seen in West Africa lately that they have more continuous flu circulation at low levels. And so, as was mentioned, maybe their continuous low-level circulation is what's kind of shows up brighter now that there is very low levels everywhere else.

They also -- Togo and Cote D'Ivoire and some of these countries have really done a great job doing influenza surveillance in the midst of the COVID pandemic. So it could be a little bit that there are strong surveillance activities in some of the countries in West Africa supported by U.S. investments and other investments from other countries.

DR. HANA EL SAHLY: Okay. Thank you. Dr. Portnoy?

DR. JAY PORTNOY: Great. Thank you. What we're trying to do today is to predict which strains

will be dominant next year to put into the influenza vaccine. Yet the pattern used to make that prediction has basically been broken this year because there's been very little influenza. Have there been previous experiences where flu basically vanished for a year, and does the pattern of emergence resume the following year?

Or does it reset such that maybe a different strain becomes dominant, and our predictions are therefore not valid? Perhaps one strain could survive low levels of flu better than another and re-emerge more quickly. And also, could some strains even go extinct when the levels are as low as they have been?

LTC KEVIN TAYLOR: Yeah. I will say that is a great question. I mean, we've been discussing that very question in our office here. Like, when we have such low influenza rates, are we just going to get an odd collection of flu viruses emerging next flu season just because the conditions are just so drastically different? I'm not aware of anything happening like this in the recent past.

We talked a little bit earlier about, I think, 2011-2012 being a down year, but that's nothing like what we're experiencing here. And so I don't know if we can use that as an example of what to expect, but perhaps we could. I'll defer to anyone else on the line who might be able to give their opinions on kind of this unprecedented situation we're dealing with, with flu, and what might possibly emerge next year.

I think we're all hoping that with what little data we do have we're still able to make a good estimation of what's going to become predominant. But I'd love to hear some conversation and discussion by others who might be considering this as well about just kind of the unusual circumstances this year and how that'll affect what may eventually emerge for next season.

DR. JAY PORTNOY: I guess there isn't any?

DR. HANA EL SAHLY: Okay.

DR. DAVID WENTWORTH: I can make a brief comment about that. I totally agree with Dr. Taylor. You can never predict what's going to happen with

influenza, so it's very challenging. And we're in unprecedented times with the level of circulation. And we don't know what will happen when people really start mixing more and the viruses have to compete with each other for fitness advantages.

But I'd also reiterate that we're not only predicting what will circulate. I think this is one of the fallacies that gets proposed in the press and everywhere else. We're using multiple factors to understand what represents the greatest risk to the human population. And oftentimes, that is the new variant that is going to predominate.

But what we know about influenza is that many variants co-circulate every season. And the more we sequence the virus genomes of many, many specimens the more we know that's true. And we talk about flu viruses like they're one virus when, in fact, an individual is infected with many different variants simultaneously because of the mutation rate of the virus.

So when I show you that human serology data

and we look at vaccine effectiveness data, we're also looking at what represents a risk. And where human sera is low across many age groups may be a predictor of what can predominate but also is a predictor of what represents a great risk to the population. Therefore, if we select vaccine candidates in those groups, presumably we'll be at least immunizing against the viruses of the greatest risk.

And so that's part of what went into the selection probably more so this season when you have less data on the viruses circulating. And the viruses that are circulating -- it's a great question that you had -- and the viruses that are circulating are different regionally. So that's one of the challenges. Over. And I would just also add that any flu vaccination is better than no flu vaccination.

DR. HANA EL SAHLY: Dr. Kurilla?

DR. MICHAEL KURILLA: Thank you. Kevin, I'm curious about -- I don't know why my camera is not working now. Kevin, I'm curious about how does the vaccine effectiveness you measured this year compared

to prior years with DoD? And how well does that align with CDC estimates in the past of overall vaccine effectiveness?

LTC KEVIN TAYLOR: Yeah. Good question. So this is comparable to what we see in DoD each year. I'll also note, though, that often with our vaccine effectiveness estimates they are typically lower than what we see for estimates for the broader U.S. population. And so there could be some reasons for that. I had kind of mentioned a little bit in my limitations slide about how the prior -- high rates of vaccination years prior might influence how we -- our ultimate calculation of vaccine effectiveness for a current year's vaccine.

But I will, yeah, again just kind of mention and reiterate that typically what we see in our vaccine effectiveness estimates are lower than what we see for the general U.S. population. So I would anticipate if we were able to do that for the general U.S. population this year, you would probably see something higher than what I reported there.

DR. HANA EL SAHLY: Okay. Dr. Holly Janes.

DR. HOLLY JANES: Thank you. I wanted to follow up -- following up on Dr. Portnoy's question and interrogate just a little bit further in the implications of -- Dr. Wentworth, you mentioned that the cross protection that the parents in the serology data that you presented earlier. And what might we speculate would be the potential impact of having essentially missed a flu season? Might we expect a lower benefit of cross protection when the viruses emerge and just following up on that in terms of specification about potential efficacy or effectiveness of the flu vaccines for the 2021 season?

LTC KEVIN TAYLOR: Yeah. So you're asking about the cross protection from prior vaccine for coming flu season? Is that what you're getting at?

DR. HOLLY JANES: Yes. I mean specifically when these viruses emerge, it's very difficult to anticipate what might emerge. But I guess a hypothesis might be, I suppose, that the viruses that emerge might be -- people have not largely been exposed for a year.

I don't know what the vaccination rates were last year. But might there be lower levels of memory immune responses to these viruses when they do emerge, and how might that influence the epidemic that we see in the 2021 season?

LTC KEVIN TAYLOR: Yeah. Oh, I see what you're saying. Okay. Yeah. And I don't know if I can really provide a great answer for that. I don't know. I see here -- I think I saw Dr. Wentworth popping up there. If he wants to chime in again, I certainly will defer to him whenever I get an opportunity because I know he's going to have something much more intelligent to add than I. So, Dr. Wentworth, do you want to mention something?

DR. DAVID WENTWORTH: Well, I think I'd agree with you. I think we don't know, again, if the low-level circulation not stimulating -- like, many people might get a common-cold-like phenotype with a low-level circulation of flu. And I think what you're asking is has this reset everybody's antibody level to a lower level, and could we be in more trouble? I guess my one

comment would be I don't know.

And the second part of it would be if you get vaccinated, though, we would hope that that would stimulate immunity from the prime of the vaccine, as well as if you have memory responses from previous seasons, it would stimulate some of that memory. So I think that since we don't know what will happen, if there could be a low level of population immunity as a whole, the vaccine should help prevent that kind of a bigger epidemic because of that low-level immunity. So what I'm saying is I think the vaccine will induce immunity even if you haven't seen flu in the previous year because you've seen it in years past, and you've been vaccinated. Many people have been vaccinated previously. Over.

DR. HANA EL SAHLY: Okay. Thank you. I think we're going to have time for one more question. We're a little over time. So Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you. I just had a question related to -- we heard a little bit earlier about vaccine usage, so you talked about efficacy. We

heard -- and I didn't know if it was related only to the United States -- but the rates of vaccination are fairly similar this year or this season as opposed to the previous seasons. Is that the same for around the world, globally, and how much of the population globally actually does receive a vaccination? And how does that impact what strains would then circulate?

LTC KEVIN TAYLOR: Yeah. I'm sorry. I don't know globally in terms of what vaccination rates are for this year. Yeah. I can certainly speak more to what we saw in DoD. As I mentioned in my slides, our vaccination rates in the group I presented on is very high because it is a compulsory vaccine for active-duty military. And that's the same year in and year out. I cannot, though, speak too much about what the vaccination rates are globally. I apologize, sorry about that.

DR. HANA EL SAHLY: Okay. Thank you. So thank you, Dr. Kevin Taylor, for presenting these data. Next on the agenda is Dr. Manju Joshi, lead biologist of the Division of Biological Standards and Quality,

Office of Compliance and Biologics Quality at CBER. Dr. Joshi.

CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS

DR. MANJU JOSHI: Thank you for the kind introduction. So today -- I am Dr. Manju Joshi from the Division of Biological Standards and Quality Control, which we refer to as DBSQC, and Office of Compliance. And I will give comments here giving you an idea about the candidate vaccine strains and potency reagents for '21-'22 Northern Hemisphere influenza season.

In my presentation, I will go over the WHO virus recommendations for the upcoming seasonal influenza vaccine for '21-'22. I'll go over the available potency reagents for the recommended components. And there'll be a couple of slides where I'm going to be emphasizing on what kind of a plan we do have for '21-'22 Northern Hemisphere season and a couple of key general comments. And let me make it

clear that those couple of slides will be more to the advantage also for my communication with the vaccine manufacturers in the audience. So I think for me, this is one chance to tell them about certain expectation and things we would like to have to run the campaign smooth.

So as far as in terms of A of H1N1 target concerned, the WHO recommended virus for '21-'22 Northern Hemisphere season vaccine is different from '20-'21 season but is the same as those recommended for '20-'21 Southern Hemisphere season. WHO has recommended that A/Victoria/2570/2019pdm09-like virus be the candidate that's the recommended strain for egg-propagated vaccine. And for cell propagated or recombinant vaccine, WHO recommendation is for A/Wisconsin/588/2019pdm09-like virus. In the interests of time, I'm not going to go over the list. But the list of all the candidate vaccine viruses that are available for the strains can be accessed at the WHO website, which I have listed at the bottom of the slide.

So if the Committee approves the use of the recommendation made by WHO, let's look over what is the status of the potency reagents for the strains. And if we look at the various reagents available for H1N1 strain, yes, this strain was recommended for Southern Hemisphere. All the other (inaudible) produced the reagents. And I have listed all the reagents available. We have egg-based reagents available from CBER, as well as from TGA and NIBSC in U.K. Similarly, CBER had prepared the reagent for cell base for one of the candidates, which was A/Delaware/55/2019.

So coming to the H3N2 strain in the vaccine, WHO recommended that for '21-'22 Northern Hemisphere season vaccine, the recommendation will be different from '20-'21 season, as well as different from '20-'21 Southern Hemisphere season. And as previously was pointed out, this time the WHO recommendation for egg-propagated vaccine is for an A/Cambodia/e826360/2020-like virus. And similarly, the same recommendation is for the cell-culture-propagated as well as for recombinant vaccine.

And again, the candidate vaccine viruses, the whole list can be accessed at the WHO website. But I'll just briefly mention here, since this is a new strain, absolutely. So currently for the CVVs, which are for antiviral vaccines, will include A/Cambodia wild type virus, as well as IVR-224 reassortants, which are available from WHO CCs and from NIBSC, UK.

The second, so antigenically similar virus, is the A/Tasmania. And both wild type and IVR-221 has been recommended as a candidate vaccine virus. And they are also available from the same sources. Similarly, for cell-culture-based CVVs which are antigenically like A/Cambodia are available for both A/Cambodia, as well as for A/Tasmania/503 virus. And they available from VIDRL in Australia. This isn't a new strain. And as far as the potency reagents for H3N2 component is concerned, we here at CBER will work with other essential regulatory laboratories and manufacturers to prepare and calibrate the reagents for measuring the potency of A/Cambodia(H3N2)-like component of the vaccine produced using different

platforms.

When looking at the Influenza B, WHO recommended virus for 2021-‘22 Northern Hemisphere season for both trivalent and quadrivalent vaccines is same as for the ‘20-‘21 Northern Hemisphere and ‘20-‘21 Southern Hemisphere season. But for egg-propagated vaccines, WHO has made the recommendation that B/Washington/02/2019-like virus and B/Victoria/2/87 lineage be the components of the vaccine. And similarly for the cell-culture propagated or recombinant vaccine, the B/Washington-like virus has been recommended. Again, the complete list of different available candidate vaccine viruses can be found at the WHO website listed here.

This vaccine component has been going on for last few seasons. Reagents are available for B/Washington from various ERLs. We here at CBER have prepared the B/Washington represented in the (inaudible) for use in combination with antiviral vaccine as well as for B/Darwin/7/2019, which is a candidate vaccine flu virus for the cell platform. And

CBER had also (inaudible) the reagents for B/Washington for a recombinant platform. So reagents -- and other ERLs (phonetic) also have some of the reagents available.

Coming to the second B component in vaccine for quadrivalent vaccine, the WHO recommends that for 2021 Northern Hemisphere season for the quadrivalent vaccine, the recommendations will remain the same as those for '20-'21 as well as for '20-'21 Southern Hemisphere. So -- and eventually happens that once again we have the B/Phuket/3073/2013-like virus recommended for both egg-propagated vaccine as well as for cell culture and recombinant vaccine. And the B/Phuket has been with us for a long time as (inaudible). Then the various candidate vaccine viruses are listed again on the WHO site. And the list always gets updated as the new viruses become available.

Coming to the potency (inaudible) reagents available for the B/Phuket-like viruses from the Yamagata type B lineage, pretty much all the ERL have

met after (inaudible). And a variety of reagents are available from each ERL. As far as CBER is concerned, we do have a B/Phuket representative reagent and antisera for B/Phuket wild type virus for egg platform.

We have two different reagents for cell-type platform, which are one for the B/Singapore/INFTT-16-0610/2016-like virus and for B/Utah. CBER has also prepared a reagent for B/Phuket for use in combination with the recombinant platform.

So this was a (inaudible) to the candidate vaccine viruses and available reagents. But how do we go on to create a vaccine campaign and make sure the vaccines are available to the public in a timely manner? This is the slide I mentioned that I would like to address more to the stakeholders and manufacturers.

Now, I would like to address to them to say that we would like that manufacturers provide us information in regard to the strains they will be using, a particular candidate vaccine virus, what kind

of reagents they are planning because some of the reagents are already available, both antigen and antiserum. And the main reason for asking these things is that this is very important for us in DBSQC to plan our flu program, as well as this involves the reagent calibration activities.

If the reagents our manufacturers are using from outside, some other ERLs, we have to make sure that we find a way forward for getting those reagents. We have to have the whole program in place for doing the monovalent testing and the complete lot release testing. And I make this appeal every year. And everybody has been really cooperative about this. And I think that was the reason why we were able to successfully do a lot of things even with the pandemic situation and all the social distancing regulations in place. So thank you, all the manufacturers, for that.

And lastly, a couple of general comments I would like to make is manufacturers should remember that only CBER authorized reagents should be used to test potency of vaccine marketed in the U.S. We are

always open, so you can always get in touch with us, consult with us. And we will guide you through that.

When it's a time concern, this is a requirement for them to submit monovalent samples. They must be submitted to the DBSQC. And please email me -- my email address is here -- regarding the dispatch of samples, your test results, et cetera. Copy them to Dr. Shahabuddin and Dr. Eichelberger. I have included their emails on the left.

If you have any inquiries regarding CBER Reference Standards and Reagents, their availability and shipping, please contact CBER Standards at CBERshippingrequests@fda.hhs.gov, and you'll be helped on that. And lastly, I would like to say that, please, we are always open to your feedback. Send all your feedback and comments on the suitability or use of the reagents provided and any other aspect of our services to the CBERinfluenzafeedback@fda.hhs.gov mailbox. It does have the address up here. We'll be happy to read it. And we would like to know how things are going.

So I think with this, thank you very much.

And I can take any questions.

DR. HANA EL SAHLY: Thank you, Dr. Joshi. Any of our colleagues on the Committee with questions for Dr. Joshi? If so, please raise your hand in Adobe. Yeah. I don't think I see questions. Thank you, Dr. Joshi.

DR. MANJU JOSHI: Thank you.

COMMENTS FROM MANUFACTURER REPRESENTATIVE

DR. HANA EL SAHLY: Dr. Lauren Parker from AstraZeneca will next give comments from the manufacturers' perspective. Dr. Parker?

DR. LAUREN PARKER: Hi, good afternoon and good evening, everyone. Thank you for the introduction. I'm really pleased to be able to be here today in the virtual space, or my kitchen in Liverpool in the U.K., to give this presentation on behalf of industry, in particular, the influenza vaccine manufacturers that supply the U.S. market for the Northern Hemisphere influenza season.

I'd just like to take this moment just before I go through the presentation to say thank you to my industry colleagues Bev Taylor, Elizabeth Nordmeyer (phonetic), Sam Lee, and Penny Post for their support and help putting this presentation together and further critical review of the content. So what I'm going to talk about today is our industry perspective looking back over the 2020-21 flu vaccine supply manufacturing campaign.

Okay. Disclosure statement from myself. As you're aware, I am an employee of AstraZeneca. I work at our Liverpool site in the U.K. And I am the scientific lead of our live attenuated influenza vaccine strain development program. My disclosure is I do own shares in the company.

Okay. So influenza is an often underestimated disease, and it can be serious. It can cause significant morbidity and mortality rates and is often quite -- it's an economic burden. It is difficult to measure this, but it has been showed to be a significant economic burden. And the best way to

prevent influenza remains vaccination. So for a flu vaccination campaign to be successful, it really is a balancing act.

So there's, I would say, three overarching areas which need to be well balanced. They need to work smoothly together for us to have a successful campaign. So, of course, we need well matched vaccine component strains which recognize and protect against the circulating influenza strains. Manufacturers need to be able to supply sufficient quantities to support the recommendations and increase immunization rates where we can. And, of course, all of that needs to be available in a timely fashion before the upcoming influenza season.

So it really does take a team to beat influenza. There are a lot of moving parts to all of this. And everyone here is involved in some way. And in industry, we quite often like to refer to the analogy as like a relay race. So if you think of a relay race, you've got multiple runners at different points along the track running at speed. They're

handing off batons to the next runner while they're already running.

So if you think of the collaborating centers or the ERLs or the high growth reassortant labs as the first runners, manufacturers will be the first receiving runners. And we start running even before we've had that baton handed to us. And generally, that's us beginning our manufacturing campaign at risk. So in order for us to be able to supply to the market at the beginning of the vaccination season, we need to begin manufacturing our commercial bulks prior to the WHO recommendation announcement.

And along the relay racetrack, there are some interesting hurdles for us to jump over as well. There's multiple batons, multiple providers, and a lot of potential hurdles. So a relay race is a really nice way of thinking about it. Also, I'm a fan of thinking about it like trying to build a plane while flying it at the same time.

So this then moves me nicely onto the hurdle looking back at the 2020-21 season. I'll just start by

commenting on the last hurdle or the first hurdle in the slide, whichever way you're looking at it, which is unexpected or late changes. So this actually isn't something that we encountered in the 2020-21 season. But we have encountered this before. And I just wanted to keep it on there as a reminder as it can have a big impact to the manufacturing and selection campaigns and getting things to market ready for the immunization. So manufacturing timelines and the Nagoya Protocol, which I'll talk more specifically about at the end of the presentation, these are hurdles that like to throw themselves in our way every season.

The manufacturing timelines, one, was off its base a bit more this season because of the COVID-19 pandemic and the increased amount for vaccines. But overall the COVID-19 pandemic is just -- it's completely thrown us into uncharted waters and uncharted territory. And it was multiple hurdles all stacked really closely together.

So some of you will be familiar with this slide. We have shown it before. It's just a nice

timeline summary of the annual seasonal flu vaccine manufacturing timeline to supply the U.S., beginning with the top blue arrow just under March, which is the VRBPAC strain selection ratification. So I'm not going to go through every single part of this slide. I just want to call out a few highlighted points for it.

So a big point here is, essentially, it takes around six months to manufacture, release, and distribute the required number of doses for the season. So if we look back at the 2020-21 season, over half a billion doses that were required to be produced and distributed globally -- and that was not just from one vaccine platform or one vaccine technology. It's three different vaccine technologies. So we've already discussed cell versus egg versus recombinant. And then the egg vaccine is split farther into the inactivated influenza vaccine and the live-attenuated influenza vaccine.

The vaccination period itself is quite rigid. It's quite inflexible. And that's because that's -- the infrastructure is set up that way so from September

to November. And some of them are starting to be pushed out now. There's so many moving parts it would take hours to list them all and go through them all. But flu seasons are changing in their timing, and there's a constantly increasing demand.

So with regards to getting supplies to U.S. market for the previous season, it took the collective manufacturers initially six months to supply all of the first doses. And within eight months the final doses were supplied. So this just takes us onto a data summary of the numbers of doses that were distributed within the U.S. last season. So that is the graph on the left with the green data slide. And I think the graph with the blue data slide is a nice representation of the fact that, with the exception of this sharp peak seen in 2010 which corresponds to the 2009 H1N1 pandemic distribution, it's just increasing constantly.

And what's amazing and something that we should all be really proud of is that, despite all of the challenges thrown at everyone during the pandemic, the number of doses of influenza vaccine supplied to

the U.S. was greater than 10 percent higher than the previous season. And the previous season's number was already high. So just to give you some exact numbers to clarify that, as of the 12th of February this year, we supplied 193.7 million doses compared with 174.5 million doses at the same reporting period last season.

And moving on now to the Northern Hemisphere recommendations, I'm not really going to go through this. Dr. Joshi has gone through it as has Dr. Wentworth. I think most of us have in the second half of the presentation.

Just a couple of things from a manufacturing perspective to really highlight is that, because we have this extreme diversification that just continues with H3N2s -- they really are amazing -- the egg recommended H3N2 strain component has been updated for the past four seasons. And we are starting to see a lot more diversification in the H1N1s, which was highlighted really nicely in Dr. Wentworth's slides there. So we have been seeing more recent updates for the H1N1 component as well, compared to post 2009

pandemic where the recommended California/07 strain was -- it was a recommendation for several years.

So looking back in a general overview way of the 2020-21 Northern Hemisphere campaign, as we all noted, there were three strain changes updated from the 2019-20 season. The H1s were updated. The H3N2s and the B/Victoria lineage -- vaccine composition was updated as well.

Due to the pandemic and the complete unknowns of what would happen if there were co-circulation between SARS-CoV-2 and influenza and to reduce the burden on everyone's healthcare system, the increased global demand for flu vaccines was around 20 percent globally. And as I said previously, I can't remember the exact numbers, but it was around 11 to 12 percent, so greater than 10 percent overall increase in the numbers of doses actually supplied to the U.S. There's some really excellent collaborative things went on between WHO, ERLs, and industry last season which really helped the campaign feel very open and collaborative and smooth running.

So we had these -- we had biweekly, WHO industry teleconferences September to February. And the Cross Functional Working Group Influenza Hub has been fully implemented. And it's been really important and key for information sharing and for CVV updates, reagent availability. It's been fantastic, and it's a massive credit to Sam Lee and Jason Long at NIBSC (MHRA). They've really spearheaded this and got it going, and it's been fantastic.

So going back to everyone's favorite subject, the COVID-19 pandemic, so at the beginning we just had no idea how this was going to affect the campaign. And initially, there did appear to be some impact on international transport and freight. However, overall, the issues were resolved, and the impacts were very, very minor.

One thing that has continued to be of a concern is the Nagoya Protocol and the ABS, so access and benefit sharing legislation issues. These continue to be of concern. I'm going to highlight more information about that when I come to the last few

slides.

So something to -- another really positive thing to point out from last season -- I won't go through all of the specific details from this table. But this is a summary of the supply of the critical potency reagents for the 2020-21 season. There was, obviously, concern over reduced staffing levels, staff being stretched, and a reduced focus on influenza.

However, our ERL colleagues prioritized the generation and calibration of these critical potency reagents. And the efforts made by them, which were phenomenal, really fantastic, it resulted, actually, in our calibrated potency reagents being available in a very similar timeframe to previous seasons. So this was one of the things that really contributed to the supply of the 2020-21 flu vaccine manufacturing campaign being a success.

So a few of these things have been discussed at great length and are mentioned -- touched upon today already. I'd just like to briefly go over them again from an industry perspective. So obviously, increased

demand for flu vaccines, which I've said already, reduced staff numbers working, that's a problem everyone's had to deal with. There was potential for supply chain and logistical challenges, which were overcome and had a minimal impact.

Something that we were very concerned about at the start of the pandemic was could SARS-CoV-2 be an adventitious agent in the clinical isolate sent from the National Influenza Centers to the collaborating centers for expansion in cells or eggs? But colleagues at VIDRL in Melbourne and the CDC did some really neat studies and published them to demonstrate that SARS-CoV-2 is actually not capable of replicating efficiently in the substrates that we use to make our flu vaccines. So that is eggs and the qualified MDCK cell lines and (inaudible) cell line. So that was done really quickly, really great work. So we got that confirmation very early on in the season.

And, of course, something that everybody's spoken about is the massively reduced numbers of circulating flu viruses. And the numbers that we've

pulled together here really are quite sparse, I think, so a 62 percent drop in the number of flu positive virus shipments to the collaborating centers and a 94 percent drop in genetic sequences uploaded to GISAID. This is the influenza sequence and sharing platform that Dr. Wentworth mentioned earlier as well.

So you put all of that together and not only is it even more complicated and complex for the WHO to review of all the data from the small number of viruses and make a recommendation; it meant that as manufacturers we had a much smaller pool of strains to work with. So in previous seasons, as a collective we could have been looking at up to 100 wild-type strains that were investigated for their potential as a reassortment -- or reassorted and characterized. And it was just -- it was not even near that. You could probably count on two hands the numbers of strains that were available. So it presented some challenges with regard to that and to be expected given the situation.

So I've mentioned the Nagoya Protocol a couple of times already. So I'll briefly mention what it is

and why it's a concern for flu vaccine manufacturers and, therefore, vaccine supply. So the Nagoya Protocol is a supplementary agreement to the Convention on Biological Diversity. It essentially exists as a legal framework for the implementation of the fair and equitable benefit sharing prior to research and development or commercialization.

So basically, it protects biodiversity when genetic resources are utilized from different countries. So pathogens do fall into the scope of this. And each country who is a signatory to this or who has their own ABS legislation, it's their right to decide whether or not pathogens are included in that. So seasonal influenza may come under that.

So we do need to take the time to formalize any legal benefit sharing arrangements that may fall under the Nagoya Protocol. This can take a range of time depending on how complex the legislation is and what's expected of the manufacturers by the country. It can take months to actually get everything necessary in place.

And if you're -- pass your mind back to my slide at the beginning -- it takes up to six months to get the vaccines delivered. So at that start of that six months we need to already -- we need to have our seeds. We need to be getting going with release testing, making seed lots, and those kind of things. So you can see where it can be problematic. So it does offer a risk to seasonal impact -- seasonal flu vaccine supply.

And something just to point out, so there are a lot of countries in the world that actually sort of negate the Nagoya Protocol. So they don't sign up to it. And the U.S. is one of these regions, as is Australia and the U.K. So if people use an influenza virus from Scotland, A/Edinburgh or A/Iowa from the U.S., we don't hold the recipient to any of this legislation.

However, that doesn't mean that those countries are not held to it from a recipient country. So just because the U.S. themselves wouldn't actually hold anybody to these legislative rules, any resources

coming in from another state or another country to the U.S. -- that would still need to be investigated. And we would need to conduct ourselves according to the legislation in that country.

So what you can see from this table is these are the CVVs that we have worked with, developed, characterized, and, in a lot of places, manufactured into product since the 2018-2019 season. And there is also another five that have no established authorization. And what I think is good to take home from this is, if you look at the column on your right on the screen, which is the current candidate vaccine viruses that have no established authorization, it's the longest list.

So having no established authorization essentially puts manufacturers in a bit of a limbo situation. And a lot more countries are adopting this. As of the 21st of February, 129 countries have ratified and entered into the Nagoya Protocol. So it's not always clear as well. There's not a one size fits all for this.

So countries are well within their rights to create their own legislation and their own rules regarding this. It's not always clear. And often, once we've gone looking for that legal information, it's sometimes not in English. It requires long translations. So there's an ever-increasing time to get clarity and receive authorization to actually use the viruses.

So this lack of legal clarity is a real risk and concern for us in industry as manufacturers. So we could be looking at delays due to getting that required clarification, negotiating where need be, and getting the official notification costs addressed and resolved. Like I said, this is not something that we really encountered and had to actively spend a lot of time resolving for the 2020-21 season. But it is becoming an ever-increasing issue that we need to keep our finger on the pulse of.

So I will finish up now. Just to summarize, there's a continued increase in demand for vaccines but in the same constrained timeframe. Any delays or

unexpected strain selections have the potential to impact supply and, therefore, a knock-on effect on the vaccine usage and uptake. And we think that flu vaccination, of course, is of great importance. Vaccination is still the best means of preventing influenza. And because of the complete unknown landscape that we're in now with regards to flu and respiratory viruses, flu vaccination will continue to be of massive importance going into the next season as COVID vaccinations increase and things like restrictions and travel bans, social distancing -- when all of those things are lifted.

We've never been in a situation like this before. And we don't know what's going to happen. We can never predict what happens with flu at the best of times. But this is very unprecedented. So the numbers will increase. And flu immunization should remain of great importance.

And just to finish off by saying we're really pleased the COVID-19 pandemic -- it didn't significantly impact vaccine supply for the 2020-21

season. And the increased demand was met successfully, especially in the U.S. with the greater than 10 percent demand met. We did resolve any small Nagoya Issues ahead of time. And due to the amazing efforts of our colleagues in the ERL and the high yield reassortant labs, all of the seasonal candidate vaccine viruses and reagents were available in time.

And we're all in this together, right? We're all here to play our own part to ensure adequate supply of the best possible vaccines to safeguard public health and protect lives. So we're all in this race together. And thank you very much for your attention. I really appreciate it. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Parker. We will have time for a few questions. I see three questions coming up. We will begin with Dr. Michael Kurilla --

DR. MICHAEL KURILLA: Thank you.

DR. HANA EL SAHLY: -- questions for Dr. Parker.

DR. MICHAEL KURILLA: And my camera is still

not working. Lauren, two questions, there's a tremendous amount of pressure on vaccine manufacturing right now for COVID. So what's going to be the impact upon flu vaccines and not just manufacturing but fill, finish vials, stoppers? In addition, there's concerns about having enough syringes. How are you factoring all this into the impact on flu -- the next seasonal production?

The other question is do I understand you correctly with regard to Nagoya that, if China had elected, they could have said, "Nobody else could use this sequence, and we will be the only people who will make vaccines off of this sequence. We're not going to let any -- we're not going to let the international community participate?" Is that a real threat or a risk from this that could have happened? We would have had to have waited for a variant to arrive so we could have said we had something different?

DR. LAUREN PARKER: Both excellent questions. Yeah. I'll answer your first question first -- well, as best as I can anyway. So things like the impact to

supply chain and actual physical components to the vaccines that we need, all of that is -- and again, I'm speaking for the industry, not for representatives. I'm representing, in particular, my knowledge from what is happening in the U.K. at the moment -- is that all of that stuff is sort of lobbied and looked at from a government level and a public health infrastructure level to ensure that everything is available, whether that means massively upping the manufacturing of syringes, the vials, all that type of thing. I'm sorry I can't be more specific about that one.

With regards to the Nagoya Protocol there, there was a lot of work done up front by colleagues at the WHO Collaborating Centers with viruses from China and Hong Kong. And it's very clear now that we have a system and a process in place, and we know how to deal with those things. I honestly wouldn't like to comment on whether or not it would have been a case of "No, we're not going to let you use that. We're going to do that."

I just wouldn't like to comment on that at

all. And it would have just -- there -- a lot of negotiations which has been done. But with regards to risks and threats, I think that from a manufacturing point of view Nagoya and ABS is one of the biggest that we're facing.

DR. MICHAEL KURILLA: Thank you.

DR. HANA EL SAHLY: Dr. Cody Meissner.

DR. CODY MEISSNER: Yeah. I wonder if you could comment on this? Over the past year, we've seen such dramatic improvements in the technology of vaccine development using adenovirus vectors, obviously, and messenger RNA platforms. And they offer the potential of much more rapid development of vaccines. Can you comment on where you think this is going to go? Will AstraZeneca -- will other companies begin to look at these platforms as a source of providing influenza vaccines?

DR. LAUREN PARKER: Sure. I think -- well, before I answer, what I'll say is that I will be answering this from probably more of an AstraZeneca point of view because, obviously, I can speak for them

on this. But I do think that -- I don't like to say that there's been an upside to the pandemic at all. But I do think it's been phenomenal to witness the scientific and medical community coming together and achieving what they did in 10 months to make a vaccine.

Like, our lockdown in the U.K. started about a year ago, and I had my vaccine three weeks ago. It's incredible. And I think with regards to what we thought we knew about how vaccines needed to be made and rigid -- our ideas have changed of them. And I do think that demand will drive what is needed to be supplied.

But the potential for some really amazing, fast, new technologies are absolutely there. And I won't be surprised to see AZ and my other industry colleagues really get their teeth into this as well. Because this is something that will help us in the event of an influenza pandemic. Using eggs as a platform to make our rapid response pandemic monovalent is so problematic. If you have a big cell culture platform or a plug and play mRNA or adenovirus vector

platform, then absolutely it's the quickest way to respond. So I think we will -- I'm hoping that we will see some really exciting moves forward in the vaccine industry over the next sort of 5 to 10 years.

DR. HANA EL SAHLY: Okay. Thank you for this hopeful note. I think on this hopeful note we will end the morning session.

DR. LAUREN PARKER: Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Parker. Next on the agenda is our lunch break, 45 minutes. So it's a little before 1:00 p.m. Eastern. So we will reconvene at 1:45 Eastern. Thank you all.

[LUNCH]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: All right. Welcome back to the 165th VRBPAC meeting. I'm Mike Kawczynski, and we will get started with the last portion of today's event. I'd like to hand it back over to Dr. El Sahly. Dr. El Sahly, take it away.

DR. HANA EL SAHLY: Thank you, Mike. So the

next item in our agenda is the Open Public Hearing. There were no formal requests for Open Public Hearing session for today, and we will be moving straight into the Committee discussion and recommendations and vote.

COMMITTEE DISCUSSION, RECOMMENDATION, AND VOTE

DR. HANA EL SAHLY: For this year, it looks like there will be changes to two out of the three subtypes: H1N1, H3N2 -- moving to Victoria/Wisconsin for H1N1 and to Cambodia for H3N2. Despite low circulation during the pandemic, it seems that these two strains will minimize the risks as Dr. Wentworth indicated of having a larger section of our population being not immune to what may be circulating.

I like that from a statistical model because we vaccinated one year against, you know, a potential two strains for A, and now we're going with two others, so a sort of hedge-your-bet kind of approach given the uncertainty around the circulation. Having said that, we're going to now move into the discussion of these

items, and, as always, please raise your hand in the Adobe function so we can begin taking Q&A.

MR. MICHAEL KAWCZYNSKI: So again, we are in our Committee discussion, so again, to our members, top of the screen, go ahead and click on your hand if you'd like to ask any questions or open up for debate. There we go.

DR. HANA EL SAHLY: All right. Dr. Spearman.

DR. PAUL SPEARMAN: I would start by saying I thought the explanations from our experts who were participating in the WHO meeting and described the changes made perfect sense. That's all I have to say.

DR. HANA EL SAHLY: All right. Thank you, Dr. Spearman. Any comments from or questions from our group? I think we still have Dr. Wentworth with us, so he can potentially clarify or answer more questions. Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you. I just wanted to say that I echo what Paul said that I thought the explanations were excellent. I mean, the surveillance even in a year where we struggled to get strains was

excellent and provided us with a lot of information. And, as you said, this is just the risk assessment, so we can't predict the future. We can only sort of surmise what might be the best protective correlates (inaudible) or protection against our population.

The only thing that did seem to be missing -- and it just goes out to our partners -- is the idea of how vaccination coverage reflects any of the surveillance that we do. Or do we pick strains that maybe wouldn't circulate in areas that actually have better vaccine coverage or sort of picking things that maybe aren't the risks that we should be looking at? That would be my only feedback, and I feel like the changes that were recommended are actually very well founded.

DR. HANA EL SAHLY: Thank you. Dr. Meissner. Dr. Meissner, you have a question?

DR. CODY MEISSNER: Yes. It just takes me a minute. Sorry. I agree with both Dr. Gans and -- that the presentation was excellent. I guess, I'll only -- my only comment is that I had hoped at this point we

would have some information about the relative efficacy of the adjuvanted vaccines versus the high dose vaccines versus cell-based or egg-based vaccines. But, obviously, that's not available because -- it's nice that there wasn't much disease, but it doesn't help us in answering any of those questions.

I guess the one question I have that someone may know here is how much trivalent vaccine is going to be available this season? It was a very small percent last year, and I assume based on the way that this discussion's been presented that there will be some trivalent vaccine this year. Over.

DR. HANA EL SAHLY: I don't know if someone from CBER may have the breakdown by -- between trivalent and quadrivalent. It looks like quadrivalent is winning the race, but...

DR. JERRY WEIR: Hmm. Oh, hi, Dr. El Sahly and Dr. Meissner. This is Jerry. Actually, I don't have the breakdown either. I think you're right. In the U.S., it is now predominately quadrivalent, and I actually don't know the numbers of who -- which

manufacturers are still producing trivalent or how much. I don't know if our industry rep might know.

There are other areas in the world where trivalent is still fairly common, though. But in the U.S., the quadrivalent has really sort of taken over the market. Thanks.

DR. HANA EL SAHLY: I have a question to Dr. Wentworth. Dr. Wentworth, maybe I'm wrong on that one, but it seems that every year the Iowa strain is an outlier in terms of antigenicity. It's presented in tables, but it's not making its way into the pool of predominant strains. Am I reading that correctly?

DR. DAVID WENTWORTH: Yeah. Do you recall which Iowa it was? One good thing about Iowa is they're one of our really good state public health lab partners like Wisconsin and Minnesota.

DR. HANA EL SAHLY: Oh, okay. I think it's under H3N2. Is that true? It's always in that table on the end.

DR. DAVID WENTWORTH: Yeah, I mean, I could -- you're probably have to pull it up to address your

question. If it's been in previous ones, it is an outlier that we selected on purpose. So we do select outliers for two reasons. One, they could be an antigenic variant that takes off, and we want to understand that. And it's also good to show that your serology panel is picking up differences. You know what I mean?

DR. HANA EL SAHLY: Mm-hmm.

DR. DAVID WENTWORTH: So sometimes like for example B/Yamagata this year -- I didn't show you data, but we picked a very strange outlier for our serology because all the other viruses reacted very well with the human sera. And it's hard to tell if, you know, you're really measuring anything. I could -- if I could look at that tree again, I can tell you -- let me just see if I can pull it up real quick. You probably deserve a better answer.

DR. HANA EL SAHLY: So it's a quasi control is what you're saying.

DR. DAVID WENTWORTH: Yeah. Sometimes we have -- like I said, Iowa's pretty popular. I think there

was a -- Iowa/6 is in co-line with B, and that's one of our outliers there, but it's an older vaccine virus. So that's -- it's only a double deletion virus, and then for the H3 -- see if I can find that one.

DR. STEVEN PERGAM: And Dr. El -- and, Dr. El Sahly, this is Steve Pergam. I think I noticed as well on the FluNet that Iowa had -- was the only state that actually had high levels of flu this year, which was sort of interesting as a side note.

DR. DAVID WENTWORTH: So actually, our H3 outlier, we did have an Iowa/60. That's an older virus. Okay. So that should have showed pretty good reactivity in a human sera, which I'm pretty confident it did. But the other one that could be similar to that one is Pennsylvania/1026, and that one did have this glycosylation site. It was lower in the human serology, but it's also -- it's very closely related to the current vaccine. And we didn't see any viruses from that particular lineage or sub lineage or subclade, however you want to define it, since about March of last year.

So, you know, that one, it just -- you never know maybe it's lurking somewhere, and it does have an advantage with the human sera, but we have no representatives of it from that group. We did make candidate vaccine viruses for that group, though. So we were prepared for that group. It just wasn't -- it didn't rise to the level of being nominated.

DR. HANA EL SAHLY: All right. Thank you for clarifying. Any of my colleagues with questions? Looks like Dr. Meissner has a question.

DR. CODY MEISSNER: Yes, thank you, Hana. One of the issues, I guess, that we all think about is whether one vaccine is more effective than others, and we really -- I don't know think there are sufficient data to address that question. But one question I'd like to ask Dr. Wentworth -- and I'm not sure I understood your -- all of your fantastic presentations. But, for example, on Slide 19 which shows human post-vaccination sera analysis, you showed one for H1N1 and H3N2. And it showed the relative GMPs to cell-propagated vaccine for the different clades. And am I

reading it correctly? If I look at the bottom line which says, for individual 65 years or older who got the high dose vaccine, there was not any clear evidence of an advantage of the high dose relative to the other vaccines. Is that a correct interpretation?

DR. DAVID WENTWORTH: I think in this particular -- this isn't a good study to look at the relative improvement from the high dose. I think, when you look at the serology, the high dose is improving things. And I don't know if there's a vaccine efficacy study like -- as you mentioned, these are clearly on everybody's mind, and I'm -- I know we're trying to do some.

When you compare elderly with -- in Japan versus elderly in the U.S., it's not a fair comparison. The Japanese sera always has a lower titer to start with, so you can see here in that particular table like you're looking at it, the Japanese sera in the elderly -- and they do have quite a few over 65, 127 at baseline, against the base 5A1 that they were immunized with. Whereas with our elderly, their baseline was

394, right?

And I think maybe the bubble chart below is a better one. So the bubble chart on the next Slide 20 -- and just so you're -- I didn't go through this probably well enough. It's a new chart we haven't shown before, but the sizes of bubble indicate the people -- the number of subjects that were at that particular titer, right? And so, if we compare the U.S.A. high dose versus the 50- to 64-year-old, which typically react better than elderly, right -- so that's the -- in the bubble chart, they're the ones right above and below each other.

DR. CODY MEISSNER: Yes.

DR. DAVID WENTWORTH: As you see they're both starting off, you know, pretty low, 25 for the 50- to 64-year-olds and 18 for the elderly, and they -- this elderly jumps up -- the 65 and older has 394 as a median instead of 171 for basically younger folks with the standard dose. So it's not a direct comparison of the age groups, but I think it does illustrate that in the immune response, the high dose is having a bit of

an impact. And we'll have to try to tease that out some more ourselves at the CDC and maybe with colleagues elsewhere and see if we can publish something on that just from the immunological standpoint. And then, maybe that would also work with vaccine efficacy studies later and be consistent or not, you know. We'll see what happens in vaccine effectiveness studies, I should say.

But anyway, I partly included this because we always have such interest in the human immune response, and I hope it's useful to the Committee to have this more detailed data than just the statistical analysis, which tries to sum up a lot of data from different people. And of course, some people react, you know, quite well to the vaccine, and others don't have a strong reaction. And that's -- you know, I don't have any explanations for that.

DR. CODY MEISSNER: Thanks. Just --

DR. DAVID WENTWORTH: But I'll check. I think I have that high dose in a couple of these bubble charts, though.

DR. CODY MEISSNER: Yes. Yeah. No, it's very interesting the way you've broken down the serologies, so thank you because that's a terrific amount of work.

DR. DAVID WENTWORTH: Thank you.

DR. HANA EL SAHLY: In terms of feedback, that slide where you have the reactivity patterns of the antisera on the cartography was also very informative, so thank you for that, too. Dr. Weir has his hand up for a question.

DR. JERRY WEIR: Yeah, I just wanted to follow up on that question just a little bit. It is true, Dr. Meissner, that there are not very many head-to-head comparisons of vaccines, but, in the case of the high dose, I remind you that that is one that we have actual clinical efficacy of the high does versus the standard dose from the same manufacturer. So that was shown to be more efficacious than the standard dose.

And I'm pretty sure that there have been effectiveness studies in subsequent years that also backed up that data. So that is one -- that is one vaccine for which we do have pretty good data that it

is more effective than the standard dose from the same manufacturer.

DR. CODY MEISSNER: Thank you. Thank you for that. Am I still on?

DR. HANA EL SAHLY: We can hear you.

DR. CODY MEISSNER: Oh. Thank you. Yes. Thank you, Dr. Weir, for that but as I remember, it was a pretty small benefit from the high-dose vaccine relative standard and probably not a sufficient basis to recommend one vaccine over another. Although, if you have equal choice, the high dose -- you're in an older age -- the high dose vaccine may make sense, but is that a correct interpretation of that data?

DR. JERRY WEIR: I seem to remember it a little differently. This was -- the high dose was first -- if I remember right, the high dose was first tested -- I think it was through accelerated approval and shown to have a much better, significantly higher serological response, and then the follow-up efficacy study showed that or demonstrated it. So I think it was fairly compelling.

DR. CODY MEISSNER: Okay. And so then, I guess, it's not FDA's responsibility to mention vaccines, but I guess a question then becomes at what point does ACIP recognize or acknowledge one vaccine's preference over another in a certain age group? That's just a thought, not a question, unless, Hana, you want to comment on that?

DR. HANA EL SAHLY: I think that the ACIP does make differential recommendations for different age groups. They've always done that, and they reviewed the data every year. The most recent change we've seen is with the LAIVs, you know, being preferential than not being preferential, so they do weigh in on the matter on a regular basis.

DR. CODY MEISSNER: Yeah, but not on the high dose, I don't think.

DR. HANA EL SAHLY: I think the high dose as well, but I'll look it up and get back with you on that one.

DR. JERRY WEIR: Yeah, I'm sorry. I can't --

DR. DAVID WENTWORTH: Yeah, I can't remember.

DR. JERRY WEIR: I can't remember either.

DR. HANA EL SAHLY: But I want to say it is, but I'll get back to you on that one. Dr. Offit has a question.

DR. PAUL OFFIT: Right. Thanks. So it is -- just to get back to what Lisa Grohskopf had alluded to because I just want one more piece of information. It is striking how little respiratory virus illness we see this year. I mean, we -- you know, not just flu. Certainly in our hospital, respiratory syncytial virus, human coronaviruses, we don't see it.

And so my question is, obviously, it's likely to be multifactorial. But, if you look at societies like, say, Japan that do mask in the winter months but don't restrict travel or don't close schools or don't really even socially distance, do those societies that choose to wear a mask in the winter -- do they have lesser rates of respiratory illnesses like flu and others? Do we know that?

DR. HANA EL SAHLY: I'm not familiar with any data around this matter, but I must say whatever

measure used to be taken in previous years doesn't even begin to compare to the measures we've taken in the last year.

DR. PAUL OFFIT: It's remarkable. This is the best vaccine ever. You know, I mean, it's (inaudible).

DR. HANA EL SAHLY: We cannot make people mask around the seasonal flu, Paul.

DR. PAUL OFFIT: No. So there are no data -- not data on those societies -- South Korea, Japan -- where they tend to wear masks for it. We don't know that. Is that true?

DR. HANA EL SAHLY: I don't know that. Are any of our colleagues familiar with any data?

DR. PAUL OFFIT: Dr. Wentworth, do you -- any information on this?

DR. DAVID WENTWORTH: I don't have -- I don't know that answer either. I'm sorry I can't help you. The only thing I know that kept circulating this -- from respiratory viruses from my interactions with public health labs have been rhinoviruses. So rhinoviruses -- so that's kind of telling that the

system was working, and they were detecting things to me. But they weren't detecting, as was already mentioned, respiratory syncytial virus, coronaviruses of other -- you know, like 229E or OC43 or influenza viruses A or B.

So I think there are studies -- you know, I didn't want to get into all this. Certainly, it's not part of my talk, but there are also studies about viral interference and the role that that can play. Clearly influenza viruses interfere with each other, and that makes a lot of sense because you have a lot of common epitopes across all the internal proteins, and you emulate interferon and a lot of cross protective non-neutralizing antibodies.

But I don't know -- you know, I think as Dr. El Sahly pointed out, it's just too hard to tell with so many factors at the same time, and I don't know of studies specific to countries that mask more frequently, you know, if it would be different there. You know, they have high density populations, so maybe if they weren't masking, their flu seasons would be

even worse. But I don't know the answer, sorry.

DR. PAUL OFFIT: All right. Thank you.

DR. HANA EL SAHLY: That's interesting, David, that you are also seeing that the rhinovirus cases a bit more than the others because that's been the experience here as well. Okay. Dr. David Kim has a question.

DR. DAVID KIM: I'm going to step back from influenza types and subtypes and ask a broader question of Drs. Wentworth and Weir. You know, the number of specimens that were tested for from the current or the past influenza season decreased by an order of magnitude. So we're talking from thousands of specimens being available to mere hundreds, and the WHO consulting meeting that Dr. Wentworth -- that you presided over, surely, that must have figured into the discussion that you had. You had, relatively speaking, a fewer number of specimens from which strain discussions could take place. And out of that discussion, were there concerns that were put forth by any of the consulting membership that the much smaller

number of specimens from which you could derive information was an issue?

DR. DAVID WENTWORTH: Hi. Yeah. I'm not sure if you can see me. All of a sudden, my camera seems to -- it doesn't show myself, but I hope you can hear me. Yeah, of course, we discussed that at pretty significant lengths because the lack of viruses, particularly in certain geographic regions where all of a sudden you have no information, really does, you know, limit your ability to understand what the breadth of variation that's continuing to circulate is.

I mean, one of the prevailing ideas is that, with so many viruses from some of the certain clades circulating before the COVID-19 pandemic, that we're pretty fit in our population. It's almost guaranteed that some of those will make it through the COVID bottleneck, and those would be viruses quite similar to what was circulating, say, in the spring of 2020, right? And then, they would almost reset and start from there.

Another, of course, hypothesis is -- or a

train of thought is that the ones making it through this bottleneck are quite advanced and divergent, and that could be why we were seeing some of the unique influenza B viruses that were really low proportions before that I commented on that 150K group. And also, you know, certain countries still had a pretty strong flu season in Asia, and Cambodia was one of them. And there we saw, you know, some evolution of the H3, but not, like, dramatic. You know, the Bangladesh have more substitutions than those in Cambodia.

So certainly, it entered the discussion, and, as I tried to point out, evaluating human sera, you know, is always important, but this season more so because, with that limited data set, you really want to understand which of these viruses that are circulating, you know, escapes that immunity the most from the previous vaccine or previous infections. And so I think that, you know, that's about all I can say about it. It does raise the uncertainty.

The other thing I just -- I think I would point out is, in the past, you know, flu probably

hasn't changed its dynamics much, but we certainly didn't have as much characterization of viruses going on in the past, right? We just didn't have the depth of surveillance that we do now. We didn't have the NGS, the next generation sequencing. We didn't have a variety of things.

And the vaccine strains changed less frequently, right? It wasn't until they were really perceived as a large antigenic drift -- that was the big driver of change. And now it's this combination of genetics and human serology in addition to some antigenic drift information from ferrets that help derive that strain selection.

So I think the conservative approach is to not change, and then, when -- the change would be when you have a strong feeling that there's a greater risk by this new group of viruses than there would be if, you know, we stuck with the same vaccine. And that's really, I think, about what I could say to comment on that. But certainly, everybody is well aware, and that's why I really have to thank all our partners

because they really went out and looked for influenza, you know, to help support this activity because they had to find the few positive stuff and get them into the right places, get them shipped to right laboratories.

Normally, that just occurs so easily. You don't have to work with epidemiologists on the ground in Asia to try to move things to, you know, a central, national influenza center or anything like that. They just kind of appear. So there was effort to produce the viruses, even though it was the limit ones that were available.

DR. DAVID KIM: I must say that discussion must have been painful at times because of the lack of sources from which you could have a robust discussion.

DR. DAVID WENTWORTH: Yeah.

DR. DAVID KIM: Congratulations all the same.

DR. DAVID WENTWORTH: Thank you.

DR. HANA EL SAHLY: Good point. I do not see any members with questions raising their hands in the Adobe. That probably ends the discussion portion of

our meeting. I turn it now over to Kathleen Hayes, DFO, who will review the voting process and conduct the vote for today.

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. So, for the voting portion of today's meeting, our members and temporary voting members, as you'll see on the side coming up, excluding the industry representative, will be voting in today's meeting. In regard to the process, Dr. El Sahly will read the final question aloud for the record, and afterwards all members and temporary voting members will cast their vote by selecting yes, no, or abstain.

You'll have two minutes to cast your vote after the question is read. Once all the votes have been placed, we'll broadcast the results and then read the votes aloud for the record. And just please note that once you've cast your vote, you can change your vote within the two-minute timeframe, but once the poll has closed, all votes will be considered final.

Does anybody have any questions about this before we get started? Okay. We can go to the first

voting slide, and, Dr. El Sahly, if you could please read the question.

DR. HANA EL SAHLY: The voting Question 1 for today: for the influenza A(H1N1) component of the 2021-2022 influenza virus vaccines in the U.S., does the Committee recommend an A/Victoria/2570/2019(H1N1)pdm09-like virus for egg-based vaccines, an A/Wisconsin/588/2019(H1N1)pdm09-like virus for cell- or recombinant-based vaccine? Please vote. Thank you.

MS. KATHLEEN HAYES: Thank you. So you'll have two minutes to go ahead and cast your vote.

(pause)

We have about a minute remaining.

(pause)

It looks like all the votes are actually in, so I think we can go ahead and end the pole and broadcast the results. Excuse me.

I will now read the votes aloud for the record. So we have Dr. Spearman voted yes. Dr. Cohn voted yes. Dr. Meissner voted yes. Dr. Levine voted yes.

Dr. Shane voted yes. Dr. Pergam voted yes. Dr. Kim voted yes. Dr. Chatterjee voted yes. Dr. Gans voted yes. Dr. Portnoy voted yes. Dr. Janes voted yes. Dr. Swamy voted yes. Dr. El Sahly voted yes. Dr. Kurilla voted yes. Dr. Offit voted yes. Colonel Wiesen voted yes.

And that concludes the vote for Question Number 1, so we can go ahead and proceed to Question Number 2. Dr. El Sahly, if you could please read the question.

DR. HANA EL SAHLY: Okay.

MS. KATHLEEN HAYES: Oh, thank you.

DR. HANA EL SAHLY: Voting Question 2: For the influenza A(H3N2) component of the 2021-2022 influenza virus vaccine in the U.S., does the Committee recommend an A/Cambodia/e0826360/2020(H3N2)-like virus? Please vote.

MS. KATHLEEN HAYES: Okay. And you'll have two minutes unless we get all the votes in early.

(pause)

Okay. Looks like all the votes are in. You

all vote really quickly. So we can go ahead and close the poll. And I will read these votes aloud. So Dr. Spearman, yes; Dr. Janes, yes; Dr. Meissner, yes; Dr. Levine, yes; Dr. Shane, yes; Dr. Pergam, yes; Dr. Kim, yes; Dr. Chatterjee, yes; Dr. Gans, yes; Dr. Portnoy, yes; Colonel Wiesen, yes; Dr. Swamy, yes; Dr. El Sahly, yes; Dr. Kurilla, yes; Dr. Offit, yes; Dr. Cohn, yes. And that concludes the vote for Question Number 2, so we can proceed to Question Number 3.

DR. HANA EL SAHLY: Question Number 3: For the influenza B component of the 2021-2022 trivalent and quadrivalent virus vaccines in the U.S., does the Committee recommend inclusion of a B/Washington/02/2019-like virus (B/Victoria lineage)? Please vote.

(pause)

MS. KATHLEEN HAYES: Okay. All of our votes are in for Question Number 3. Dr. Spearman, yes; Dr. Cohn, yes; Dr. Meissner, yes; Dr. Levine, yes; Dr. Shane, yes; Dr. Pergam, yes; Dr. Kim, yes; Dr. Chatterjee, yes; Dr. Gans, yes; Dr. Portnoy, yes;

Colonel Wiesen, yes; Dr. Swamy, yes; Dr. El Sahly, yes; Dr. Kurilla, yes; Dr. Offit, yes; Dr. Janes, yes. And that concludes the results for our voting Question Number 3. And we can proceed to our last voting question, Number 4.

DR. HANA EL SAHLY: Question 4: For quadrivalent 2021-2022 influenza vaccines in the U.S., does the Committee recommend inclusion of a B/Phuket/3073/2013-like virus (B/Yamagata lineage) as the second influenza B strain in the vaccine? Please vote.

(pause)

MS. KATHLEEN HAYES: Okay. And all of our votes are in for Question Number 4. Dr. Spearman, yes; Colonel Wiesen, yes; Dr. Meissner, yes; Dr. Levine, yes; Dr. Shane, yes; Dr. Pergam, yes; Dr. Kim, yes; Dr. Chatterjee, yes; Dr. Gans, yes; Dr. Portnoy, yes; Dr. Janes, yes; Dr. Swamy, yes; Dr. El Sahly, yes; Dr. Kurilla, yes; Dr. Offit, yes; Dr. Cohn, yes. And that concludes the voting portion of today's meeting.

So thank you very much. I will hand it back

over to Dr. El Sahly if anybody would like to give their rationale for today's vote. Thank you.

DR. HANA EL SAHLY: So we will go over the virtual table and ask the Committee members for any final thoughts. Michael from audio visual, I don't see the names on the screen anymore. What can I do?

MR. MICHAEL KAWCZYNSKI: There you go, Dr. El Sahly.

DR. HANA EL SAHLY: All right. Now, I can see them. Okay. So we will go around the table asking our Committee members for any final thoughts or any explanations of this vote if they wish to give one. Dr. Wiesen. Unmute it, Dr. Wiesen.

COL. ANDREW WIESEN: Sorry. I did the double mute. Sorry. My bad. Yeah, I didn't know you were going to come to me first. It's exciting.

No, I think the presentations are all straight forward. The vote was, I think, a relatively easy one. The only thing I would want to mention, number one, is I've done this for, I think, four years. I think this may be my fifth year, but I am retiring this summer.

So there will be someone else from DoD to be the temporary member after me.

And I will also remind the folks, I know there were several questions about studies about the differences between vaccines, and the DoD is doing a study looking at the difference between recombinant egg-based and -- I'm forgetting the third types now. Anyway, but, of course, that study got -- there weren't enough cases the first year, which was two years ago, and there certainly weren't enough cases this year for them to get meaningful recruitment into the study. So it has been delayed. But the intent is to see if they can come up with a relative, at least, estimate of whether there's a significant difference in how any of those vaccines work. So there will be more to follow from my successor, but at least, we realize it's an important question. we just haven't been able to get to an answer on it yet.

DR. HANA EL SAHLY: That would be great to see the data from a well conducted study on the matter. Thank you, Dr. Wiesen. We will miss you.

COL. ANDREW WIESEN: I'll miss this, too. Bye.

DR. HANA EL SAHLY: Dr. Kim. Dr. David Kim. Okay. We will...

DR. DAVID KIM: Oh, geez. I did not raise my hand.

DR. HANA EL SAHLY: No, it's for any final thoughts or comments, if you have any, pertaining to the vote.

DR. DAVID KIM: I would like to congratulate the Committee and the presenters for a well-thought out, comprehensive discussion and really making a pretty straightforward case for a relatively easy vote. I realize in preparation for today's meeting the presenters' ability to assemble the necessary information must have been so much more difficult this year compared to the years past. And for all the extra effort that went into the WHO's meeting last month as well as for today's meeting, I'd like to thank the presenters and congratulate them for really a terrific job.

DR. HANA EL SAHLY: All right. Thank you, Dr. Kim. Dr. Cohn. Amanda Cohn.

CAPT. AMANDA COHN: Hi, everyone. I just want to tell the presenters thank you for all of their work to put these together. I think this -- I know we all said last flu season that it was really critical to get vaccinated. As you could hear from the discussion today, all of the unknowns are going to be even more unknown what's going to happen next season, and so I think, you know, ensuring people are vaccinated both against flu and COVID is going to be really critical to help get us through this year and next year's flu season.

I also want to just say that this is -- the meeting last year, this was supposed to be my first meeting, the flu meeting, and I didn't come last minute because I was doing the COVID response. And it was the only -- I didn't realize it was the only opportunity I was going to have to meet all of you in person. So it's good to see you all virtually, but it's now been -- this is our second spring flu meeting with the COVID

tint of it.

DR. HANA EL SAHLY: There will be a post-COVID year. No worries. Thank you, Dr. Cohn. Dr. Andrea Shane. Please unmute, Dr. Shane.

DR. ANDREA SHANE: Okay. Thank you. Sorry. Double muted. Thank you very much, Dr. El Sahly, and thanks to the CDC and industry presenters for providing a very nice perspective in making the decision for us easy, so to speak. And the tremendous amount of data based on the information that we have was very helpful in helping us to think through the decision.

I agree we're going to have lots of challenges with trying to ensure that our children and parents and others in society continue to take advantage of receiving the influenza vaccine, but we have had a very nice discussion in reaching what I think is a good recommendation. So thank you very much.

DR. HANA EL SAHLY: Thank you, Dr. Shane. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thanks, Dr. El Sahly. Just a couple of quick comments to make with regard to

my vote, I would also like to thank all of the presenters for sharing the vast amount of data that they did, and my vote was based on the recommendations that came from the experts really in this arena. I do want to commend the people -- and this is not just the presenters but everyone who is involved -- in remaining focused on flu, which, you know, would have been easy to lose our focus on during this pandemic time. But this is our annual nemesis, and so it makes sense that people have remained focused on this. We have limited data, but what data we have do help us to make these decisions.

The second point I wanted to make was with regard to the new technologies -- and I think it was Dr. Offit that made reference to that -- that have emerged -- new vaccine technologies that have emerged, and this is really in exaltation to industry partners to focus on how those can be harnessed to make better influenza vaccines. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Chatterjee. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. El Sahly. And I too would like to thank folks from the CDC and from CBER for their always clear and very helpful presentations. I can only imagine how much work goes into it.

This year is -- it's easier in one sense and it's harder in another sense to try and anticipate what's going to happen this fall. It's unlikely that the influenza virus has mutated itself out of existence as I first heard one of our speakers today, Dr. Wentworth, say some time ago. And it's -- there may be fatigue with nonpharmacologic interventions next fall, and we may very well have variant strains of COVID-19 that are circulating as well as influenza. Hopefully, that's not the case, and hopefully, the strains that will be in the vaccine will in fact be helpful. Over.

DR. HANA EL SAHLY: Thank you, Dr. Meissner. Dr. Geeta Swamy.

DR. GEETA SWAMY: Hi there. Thanks, everyone. I don't have anything further to add other than to say it will be interesting to see in the fall as research

gets forwarded if we are able to measure what components of the pandemic prevention strategies may actually still be helpful. I think it will be hard to make this the best vaccine as Dr. Offit mentioned, but, if we can do things about, you know, avoiding interaction when individuals are still -- are symptomatic with illness, and quite frankly a lot of remote working is, I think, going to go forward in settings where that's a possibility.

And I raise that because we may end up seeing potential worsening disparities when we see incidents of other illnesses such as respiratory conditions that may not be about mortality but other morbidity situations. That will be interesting none the less. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Swamy. Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you very much, Dr. El Sahly. I just had a couple of thoughts. I, you know, had mentioned before that I thought that the presentations were outstanding. One of the issues that

I thought was really well articulated by Dr. Wentworth is that each year that we meet -- and, again, I've only done these a couple of times -- it does feel like the Agencies are very responsive to some of the information that we have wanted, and he was able to provide us with new data sets that I thought were enhancing our ability to really understand this. And I just really wanted to say that we appreciate the responsiveness of the individuals who have been working with us in trying to give us information that we feel we need. As I mentioned before, it would be really wonderful to understand just a few other data points as I mentioned previously.

The other issue that I think is very important, we talk about vaccine efficacy, and we all see -- and we've talked about how we look forward to using some of the information that we've learned in the pandemic. And I think we shouldn't lose sight of that. And I was very grateful also for the industry talking about these partnerships that are going to bring us into the future, and we should really not revert back

to anything that we had done in the past.

In terms of vaccine efficacy, I think it's very important we talk about sort of this idea of not getting ill or not being able to sterilize the world with these. And that's really -- I think we're going to have to start changing our expectations of vaccines. I mean, the flu vaccine that's highly effective at preventing severe disease and death and mortality as well probably the correlate that we should look at for at least the SARS-CoV-2 vaccines as well. And so I think maybe looking at it through a different lens will be really important.

And I look forward to seeing the data again next year and maybe some new information about the vaccines and the strains. Thank you.

DR. HANA EL SAHLY: Thank you. Dr. Holly Janes.

DR. HOLLY JANES: Thank you, Hana. I wanted to also just echo my thanks for the speakers and really a great -- you know, echo the appreciation for the nuanced presentation in helping us wrestle with the

very limited information with which to make the recommendations this year and the new analyses that were presented in response to questions previously by the Committee as well as just the efforts that are clearly being made to expand the ways in which we look at these data and recommendations. Thanks.

DR. HANA EL SAHLY: Dr. Portnoy.

DR. JAY PORTNOY: Thank you. Yeah, I want to thank the Committee for inviting me to participate as the consumer representative. This was my first time at this type of committee.

I thought it was very interesting as a complement and a contrast to the COVID committee, which I was on last week. Since that committee had a lot of discussion of variance, my guess is that COVID will require the same type of surveillance we saw with influenza in the future to monitor surveillance, and an annual vaccine will probably be necessary for those variants.

And this type of meeting will probably be used for COVID. Maybe they'll be combined. It'll be an

influenza/COVID committee meeting. It's hard to say. I'll be interested to see whether the COVID and influenza vaccines can be combined together into a maybe a quint-avalent vaccine of some sort because otherwise it's a lot of vaccines.

I look forward to development of the new platforms, mRNA adenovirus-based platforms, for producing virus vaccines, perhaps even influenza vaccine as we heard before. Since they were so incredibly effective for treating COVID, I wonder if the immunity and the effectiveness for influenza would be enhanced by these new platforms. It may, in fact, make it much easier to control the virus. But I look forward to seeing results of this in the future. Thank you very much.

DR. HANA EL SAHLY: Thank you, Dr. Portnoy. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Hana. No, I think overall this was a very satisfying meeting. It is unfortunate that the amount of flu available for analysis is much reduced in terms of vaccine --

potential vaccine selection, but it is a good thing that we are seeing a great reduction in influenza disease. I think the one thing that will have to be very carefully examined going forward is our surveillance given that there's a high likelihood that COVID may end up -- this COVID may end up becoming another one of the endemic strains.

I think it probably should prompt us to think about differences in terms of how we view what we typically refer to as influenza-like illnesses, that the combination of the two -- there may be a lot of unrecognized coronavirus disease that we just haven't been looking for before. So I think it will be a very important to reevaluate how we do surveillance going forward so we can accurately know the cases of flu versus corona versus other human respiratory viruses that are probably having an impact on the elderly and others with comorbid conditions. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Kurilla. Dr. Levine.

DR. MYRON LEVINE: Thank you. I would also

like to add my thanks and kudos to the presenters and in particular to thank David Wentworth for the new type of slide, the bubble slide, that he's produced that have taken a very complex amount of data and taken us a step further -- to easier to understand the interrelationships. Thanks also to Kathleen Hayes and to Mike handling the AV. For me, a technological dinosaur, this is always a stress, and I appreciate their help.

To be honest, the major takeaway that I go away with is the extraordinary fall in the number of influenza isolates despite clearly a fair number of specimens to be looked for. And I know from a number of sources that influenza along with a test for COVID are ongoing with many individuals for respiratory infection. And that fact is titillating my brain.

It implies, though, if masks and social distancing are contributing to that, why is that appearing to be less effective with SARS-CoV-2? I think maybe some interesting information may come from the U.K. where with similar patterns of masking and of

social distancing a -- their so-called "U.K. variant," which wasn't associated with increased severity or not greatly so but was clearly associated with increased transmissibility, makes one wonder if there is a true difference in the ability of these measures to intervene against influenza versus against SARS-CoV-2.

And even looking at the major strain in the U.S. and across the world of SARS-CoV-2 before the new emerging variants concern appeared, it was this subtle, you know, D614G mutation that affects transmissibility that allowed that to take over. Maybe we need to get super masks for people, and that could make a difference. But I think that's going to come down to, despite its possible effects, is getting populations to use those potentially powerful tools during wintertime. Thank you all.

DR. HANA EL SAHLY: Thank you, Dr. Levine. Dr. Offit.

DR. PAUL OFFIT: Right. I don’t have anything to add other than what other people said to sort of I guess make the point that we're lucky to have -- be

surrounded by the level of expertise that we're surrounded by which makes our decisions much easier here. So thanks again to our presenters. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Offit. Dr. Spearman.

DR. PAUL SPEARMAN: Thank you, Hana. Yeah. I'll be brief. Thanks again to all the presenters and to the organizers at CBER. I thought it was very well presented, and it made our jobs easy.

Two take aways for me, one is I think, sort of paraphrasing, flu is unpredictable. We're predicting the best we can or the experts who provided us all the information to choose the right strains. Let's hope that that works, but there is some unpredictability.

The second thing really is to, as previously mentioned, the remarkable lack of flu, the historical lack of flu is amazing. And it's an opportunity to learn what's really behind that, and like Dr. Meissner said also RSV, no RSV season that we've seen. It's just amazing, so let's figure it out. Is it all the behavioral things and changes in behavior and masking

et cetera, or is there some biological part to it, too? Thanks.

DR. HANA EL SAHLY: Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Yeah. I really don't have much to add to everybody else. I think I may be last, so I'll try to make it brief.

I just would like to say I'm really going to be interested in what happens this year with flu. We've been talking about what has happened over the last year, but going into this without a lot of predictability but from the vaccine's perspective and how social changes will be continued through the upcoming year is going to be fascinating to see. And at this meeting next year will be one of the most intriguing for me as we start planning and looking back at the year of what has happened to the flu. But thanks, everybody, for their contributions again. Great presentations by those who presented.

DR. HANA EL SAHLY: Thank you, Dr. Pergam. I'm thankful for the presenters, for my colleagues, for these thoughtful questions and deliberations. It was

at least gratifying to see that the uptake of flu and the number of doses in the United States if anything increased, which sort of was a silver -- quasi silver lining in this past year in that our attention to other public health measures continued. Given the data presented on antigenicity and the -- all circulations of what we have, I think the proposed strains make genealogic sense. And I want to thank the CDC for this large body of data that they synthesized for us every year in ever-improving fashion. And we'll wrap it up for this session. I'll turn it over to Kathleen.

ADJOURN MEETING

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. Before we close out, I just wanted to note for the record that pertaining to the voting portion of today's meeting that all four questions did have unanimous 16 out of 16 votes, so I just wanted to note that. But outside of that, you know, I just want to thank everybody for attending today. I know that lots of you

have to get up early and take a lot of time to review the material, and I just hope everyone knows that we really appreciate your contribution to the meeting. And with that, we can adjourn. Thank you.

DR. HANA EL SAHLY: I forgot to thank Marion and the rest of the members at CBER. Thank you all very much.

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. Thanks, everybody. Have a good afternoon.

UNIDENTIFIED FEMALE: Thank you.

MR. MICHAEL KAWCZYNSKI: All right. And thank you, and with that the 165th meeting of the VRBPAC is adjourned. Have a great rest of the week.

[MEETING ADJOURNED FOR THE DAY]