FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
159th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

TOPIC I OPEN SESSION

FDA White Oak Campus
Great Room, Salon B & C
Silver Spring, MD 20903

March 4, 2020

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

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Paul Spearman, M.D.	University of Cincinnati School of Medicine
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Sheldon Toubman, J.D.	New Haven Legal Assistance Association
Jack Bennink, Ph.D.	National Institutes of Health
Melinda Wharton, M.D., M.P.H.	Centers for Disease Control and Prevention
Col. Andrew Wiesen, M.D., M.P.H.	Office of the Assistant Secretary of Defense
David Wentworth, Ph.D.	Centers for Disease Control and Prevention
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OPENING REMARKS: CALL TO ORDER, INTRO OF COMMITTEE

DR. EL SAHLY: Good morning. Welcome to the 159th meeting of the Vaccine and Related Biological Products Advisory Committee meeting at the FDA. I welcome the members of the committee, the audience here with us, and the audience on the webcast. Before we begin this meeting, I will ask everyone to introduce themselves, their affiliation, and their expertise. Begin on the far end.

DR. ANNUNZIATO: Thank you. Hi, I'm Paula Annunziato. I'm with Merck, and I am in our vaccine clinical research group.

DR. BENNINK: I'm Jack Bennink. I'm with the National Institutes of Health, National Institute of Allergy, Infectious Diseases, and I'm a viral immunologist.

COL. WIESEN: Andrew Wiesen. I'm with the Department of Defense Health Affairs, preventive medicine, public health physician by training.

DR. WENTWORTH: David Wentworth. I'm the Director of the WHO Collaborating Center in Atlanta, Georgia, at the CDC.

DR. BECKHAM: There we go. Hi, I'm Tammy Beckham. I'm with the Office of Infectious Disease and HIV/AIDS Policy and Office of the Assistant Secretary for Health. I'm a DVM and specialty infectious diseases.

DR. CHATTERJEE: Good morning everyone. I'm Archana Chatterjee. I'm Chair of the Department of Pediatrics and Senior Associate Dean for Faculty Development at the University of South Dakota, Sanford School of Medicine. I'm a pediatric ID specialist.

DR. GANS: Good morning. I'm Hayley Gans from Stanford University Medical Center, Pediatric Infectious Disease, and I work on host pathogen interface related to vaccines.

DR. SPEARMAN: Hi, I'm Paul Spearman. I'm Director of Infectious Disease at Cincinnati Children's Hospital. My expertise is virology and vaccine

clinical trials.

OPERATOR: If anybody on the phone can make sure that we mute our phones.

DR. EL SAHLY: For the webcast audience or the phone audience, please mute your phones.

DR. LEVINE: Okay. Good morning everyone. Mike Levine. I'm from the University of Maryland School of Medicine where I'm the Associate Dean for Global Health, Vaccinology, and Infectious Diseases, boarded in pediatrics and preventive medicine.

DR. SWAMY: Good morning. I'm Geeta Swamy, I'm Associate Professor of OB/GYN at Duke University and do research in maternal immunization and pregnant and perinatal infectious disease.

DR. EL SAHLY: Hana El Sahly, Baylor College of Medicine, board certified in adult infectious diseases and I work on clinical vaccine development. Again, please mute your phone if you are on the line.

MS. HAYES: Kathleen Hayes, Division of Scientific Advisors and Consultants.

UNIDENTIFIED FEMALE: Mr. Toubman. Mr. Toubman, if you could please mute your phone.

DR. EL SAHLY: Can we -- can we remove them from here? If we can cut them off. Thank you.

UNIDENTIFIED MALE: Thank you.

MS. HAYES: Good morning everyone. My name's Kathleen Hayes. I'm with the FDA Division of Scientific Advisors and Consultants.

DR. KURILLA: Mike Kurilla. I'm with the National Institutes of Health at the National Center for Advancing Translational Science, Infectious Disease, Infectious Disease Product Development, and my training is in pathology.

DR. MEISSNER: Good morning. My name's Cody Meissner. I'm from Tufts University School of Medicine in Boston, and I have an interest in pediatric infectious disease and immunizations.

DR. OFFIT: My name's Paul Offit from the Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine. I'm in the Division

of Pediatric Infectious Disease with an expertise in vaccines.

DR. SHANE: Good morning. I'm Andrea, Andy Shane. I'm at Emory University and Children's Healthcare of Atlanta in Atlanta, Georgia. I'm a pediatric infectious disease physician with an interest in vaccines and neonates. Thank you.

DR. WEIR: Jerry Weir. I'm the Director of the Division of Viral Products at CBER FDA.

DR. GRUBER: Good morning. My name is Marion Gruber. I'm the Director of the Office of Vaccines, Research, and Review at FDA.

DR. EL SAHLY: Do we have someone on the phone who needs to introduce themselves? Anyone on the phone remaining? Okay. All right. Maybe later. For now, Kathleen will read the conflict of interest statement and some housekeeping items for the meeting.

ADMINISTRATIVE ANNOUNCEMENTS, CONFLICT OF INTEREST

STATEMENT

MS. HAYES: Thank you, Dr. El Sahly. And apologies for the delay this morning due to some unforeseen circumstances, but I'm happy everybody's here today and welcome everybody. My name's Kathleen Hayes, and it is my pleasure to serve as the designated federal officer for the 159th VRBPAC meeting. The committee management specialist for this meeting is Ms. Monique Hill, and she's supported by Ms. Joanne Lipkind both of whom are located outside of the room at the registration table.

The committee management officer for this meeting is Ms. Casey Stewart, and our Division Director is Dr. Prabhakara Atreya. On behalf of the FDA, the Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome everyone to today's meeting. The meeting for today has two topics. Topic number one is open to the public in its entirety and topic two is partially closed. Both meeting topics

were described in the federal register notice that was published on January 6th of 2020.

I would like to acknowledge that the press is in attendance here today. Megan McSeveney, if you could please stand up so we can identify you, please. Thank you. And the transcriptionist here today is Devin Shiple.

Before we begin with reading the conflict of interest statement, I would just like to briefly mention a few housekeeping items. To start with, if everyone could please ensure that your cell phones are on mute or silent, that would be appreciated. Also, as we are deliberating throughout the day, if you could clearly speak into the microphone and begin by stating your name; that way we can accurately record the comments for this meeting. For those participating remotely, if you could also please ensure that your microphones are on mute unless you are speaking, this will help to avoid feedback in the room. I will now proceed with reading the conflict of interest

statement.

The Food and Drug Administration is convening today, March 4th, 2020, for the 159th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as the Chair for this meeting for both topic one and topic two. The meeting today will have two conflict of interest disclosure statements read prior to each topic session that will occur during the meeting today.

In the morning on March 4th, 2020, VRBPAC will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccine for the 2020 northern hemisphere influenza season. This topic has been determined to be a particular matter involving specific parties. Related to the discussions at this meeting, all members and SGE consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those

imputed to them including those of their spouse or minor children, and for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents, and royalties, and primary employment. FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208. Dr. Paula Annunziato is

currently serving as the industry representative to this committee. Dr. Annunziato is employed by Merck. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. However, industry representatives are not appointed as special government employees and serve as nonvoting members of the committee. They are not authorized to attend any closed sessions, if held.

Dr. Penny Post is currently serving as the manufacturer's representative speaker to this meeting. Dr. Post is employed by Sanofi Pasteur. Manufacturer representative speakers may make a presentation on behalf of all related vaccine manufacturing industry and bring their perspective to the committee.

Mr. Sheldon Toubman is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee and hence do have voting privileges,

and they are authorized to participate in the closed sessions, if held.

The following are serving as the temporary voting or nonvoting members of this committee. Dr. Jack Bennink is employed by the National Institutes of Health and serves as the chief of the viral immunology section in the National Institute of Allergy and Infectious Diseases. Dr. Bennink is a regular government employee whose major area of research includes the interaction between host immunity and viruses, influenza virus evolution, and the cellular processing and presentation of viral antigens.

Colonel Andrew Wiesen serves as the Director for Preventative Medicine in the Office of the Assistant Secretary of Defense for Health Affairs, Health Readiness Policy and Oversight. As part of his government duties, he also currently serves as an assistant professor of epidemiology and primary preventive medicine and biostatistics at the Uniform Services University of Health Sciences in Bethesda,

Maryland. Colonel Wiesen is also a consultant to the Army Surgeon General.

Dr. David Wentworth is employed by the Centers for Disease Control and Prevention and serves as the Chief of the Virology Surveillance and Diagnosis Branch and Influenza Division. He is an internationally known expert in influenza virus epidemiology, worldwide influenza disease burden, and influenza virus vaccines. Dr. Wentworth is a regular government employee and serves as a speaker for this meeting under topic one. He is also serving as a temporary non-voting member under topic one.

The following are serving as speakers at this meeting. Dr. Mark Scheckelhoff currently serves as the director of the laboratory operations in the U.S. Public Health Service. He is an internationally known expert in infectious diseases. Dr. Scheckelhoff is a Commander in the United States Public Health Service and serves as the Department of Defense speaker for this meeting under topic one.

Dr. Lisa Grohskopf is employed by the Center for Disease Control and Prevention, Influenza Division. Dr. Grohskopf is a subject matter expert on influenza and influenza vaccine. Her primary work is with the Advisory Committee on Immunization Practice, ACIP, and, in this capacity, she periodically communicates with the vaccine manufacturers to the extent needed to keep the ACIP informed of matters that are important to the development of vaccine policy. Dr. Grohskopf will serve as a speaker for this meeting under topic one.

At this meeting, there may be regulated industry speakers and other outside organization speakers making presentations. These participants may have financial interests associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products, and, if known, its direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement. And their exclusion will be noted for the record.

This conflict of interest statement will be available for public viewing at the registration table, and this concludes my reading of the conflict of interest statement for the public record. At this time, I would like to hand the meeting back over to Dr. El Sahly. Thank you.

FDA INTRODUCTION

DR. EL SAHLY: Thank you, Kathleen. The introduction of this meeting will be given by Anissa Chueng who is the regulatory coordinator at the Division of Viral Products at the FDA. Ms. Chueng?

MS. CHUENG: Good morning. I'm going to give the introductions on today's VRBPAC discussions on the influenza virus vaccine strain selections for the 2020-2021 northern hemisphere. So the purpose of today's meetings is having the committee to discuss and to review the influenza surveillance and epidemiology data, genetics and antigenic characteristics of the recent circulating viruses, serological responses to current vaccines, and the availability of the candidate vaccine strains and reagents. And at the end of the presentations, the committee will be asked to make recommendations for the strain of the influenza A, H1N1 and H3N2 and the B viruses to be included in the 2020 and 2021 influenza vaccines licensed for use in the United States.

You will hear several presentations today.

The types of analysis that are used for vaccine strain selections include the epidemiology of the circulating strains. CDC will give a presentation on the surveillance data from both the U.S. and around the world. You will also hear a couple talks on antigenic relationships among the contemporary viruses and the candidate's vaccine strain.

The CDC and also the Department of Defense will give this talk. The analytical assays and tools that are used to generate this data includes the hemagglutinations inhibition test using the post-infections ferret sera. The same test will also be used to test on the sera obtained from humans who have received recent influenza vaccines. You will hear data on the virus utilization test, antigenic cartography, as well as the phylogenetic analysis of the hemagglutinins and neuraminidase genes. You will also hear reports of vaccine's effectiveness.

So the working viral seed for the production of the inactivated influenza vaccines are traditionally

isolated from embryonic eggs, and their antigenicity are characterized by the WHO collaborating centers. Starting in 2016, the use of the MDCK cell-isolated candidate vaccine virus strain was approved for the manufacture of Flucelvax, which is a cell-based seasonal influenza vaccine. The cell isolated vaccine's viruses can be derived from two approved WHO collaborating centers, and they are manufacturer specific.

The process of antigenic analysis is the same as that used for the egg-isolated vaccine virus strain. As you will hear from today's presentation, WHO recommended vaccine strain may differ from egg-based and non-egg-based vaccines. And more details regarding to these recommendations will be discussed during the CDC presentations. All working virus seeds are approved for quality and safety by the national regulatory agent authorities.

I would like to refresh the committee regarding to the recommended influenza vaccines

compositions for the 2019 and 2020. So VRBPAC met twice a year on the vaccine strain selections each year. The first meetings met on March 6th and March 22nd, 2019, and the VRBPAC gave recommendations for the antigenic compositions of the 2019 and 2020 influenza virus vaccines in the U.S.

These were the recommended strains: A/Brisbane/02/2018, (H1N1)pdm09-like virus and A/Kansas/14/2017 (H3N2)-like virus. For the B strain is a B/Colorado 06/2017-like virus which is from the Victoria lineages. For the quadrivalent vaccines, it contains about three viruses and a B/Phuket/3073/2013-like virus which is from the Yamagata lineage.

And the second meeting met on October 9th, 2019, and, in that meeting, VRBPAC recommended the antigenic compositions of influenza virus vaccine for the southern hemisphere 2020. These were the recommended strains: A/Brisbane/02/2018 (H1N1)pdm09-like virus and A/South Australia/34/2019 (H3N2)-like virus. For the B strain, a B/Washington/02/2019-like

virus from Victoria lineage -- for the quadrivalent vaccines containing the above three viruses and a B/Phuket/3073/2013-like virus from the Yamagata lineage.

To summarize where we are right now at this point, WHO met last week and made recommendations for the influenza vaccine compositions for the northern hemisphere 2020 and 2021. The WHO recommended the following viruses be used for trivalent influenza vaccines in the 2020 and 2021 northern hemisphere influenza season: for influenza A H1N1 for egg-based vaccines, an A/Guangdong-Maonan/SWL1536/2019 pdm09-like virus; for cell or recombinant-based vaccines, an A/Hawaii/70/2019 (H1N1)pdm09-like virus, a change from an A/Brisbane/02/2018 (H1N1)pdm09-like virus recommended from last season's recommendations; for influenza A H3N2 for egg-based vaccines, an A/Hong Kong/2671/2019 (H3N2)-like virus; for cell or recombinant-based vaccines, an A/Hong Kong/45/2019 (H3N2)-like virus, a change from an A/Kansas/14/2017

(H3N2)-like virus from last season's vaccine recommendations.

For the B strain in the trivalent vaccines, they recommended a B/Washington/02/2019-like virus from Victoria lineage, a change from a B/Colorado/06/2017-like virus vaccine recommendations but had the same virus vaccine recommendations for the 2020 southern hemisphere. For the quadrivalent vaccines containing two influenza B viruses, the WHO recommended the above three viruses and a B/Phuket/3073/2013-like virus from Yamagata lineages. There is no change from the 2019 and '20 northern hemisphere recommendations. As in the previous year, national or regional control authorities approved the composition and formulations of the vaccines from their own countries.

So at the end of the presentations, the committee will be asked to discuss which influenza strain should be recommended for the antigenic composition of the 2020 and 2021 influenza virus vaccines in the U.S. And these are the options for

strain compositions for the 2020 and 2021 influenza vaccines: for influenza A H1N1 for egg-based vaccine, you can recommend an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus and for cell and recombinant-based vaccines recommend an A/Hawaii/70/2019 (H1N1)pdm09-like virus. Or you can recommend alternative H1N1 candidate vaccine viruses.

For influenza A H3N2, for egg-based vaccines, the committee can recommend an A/Hong Kong/2671/2019 (H3N2)-like virus and for the cell and recombinant-based vaccines recommend an A/Hong Kong/45/2019 (H3N2)-like virus or recommend alternative H3N2 candidate vaccine viruses. For influenza B, the committee can recommend a B/Washington/02/2019-like virus from Victoria lineage or recommend an alternative candidate vaccine virus from the B/Victoria lineage or recommend a candidate vaccine virus from the B/Yamagata lineage. For the second influenza B-strain, for quadrivalent vaccines, the committee can recommend inclusion of a B/Phuket/3073/2013-like virus from Yamagata lineage or

recommend an alternative candidate vaccine virus from the B/Yamagata lineage or recommend a candidate vaccine virus from the B/Victoria lineage.

So before I finish my introductions, I would like to flesh out the questions for the committee for voting at the end of the meetings. As usual, we have four questions and one for each strain. And all of our voting are yes or no and done electronically. So this is what I have and thank you.

DR. EL SAHLY: Thank you, Ms. Chueng. Anyone has a question for Ms. Chueng? All right. Thank you, Ms. Chueng. Next is Dr. Lisa Grohskopf who is the Associate Chief for Policy and Liaison Activities, Epidemiology and Prevention Branch Influenza Division at the CDC. Dr. Grohskopf will review the U.S. influenza surveillance for this season.

U.S. SURVEILLANCE

MS. HAYES: Dr. Grohskopf will be

participating via phone so if there's a way we can try and unmute them that would be great.

CAPT. GROHSKOPF: Hi, can you hear me?

MS. HAYES: We can.

CAPT. GROHSKOPF: Excellent. Thanks. Okay. So this talk has two parts. One is an overview of the current U.S. influenza activity from the CDC surveillance systems. And in recent seasons, I've also been asked to present the preliminary U.S. flu VE results, so I have that as the second part.

Moving on to the second slide, we'll talk about U.S. influenza surveillance first. These slides are a courtesy of Lynnette Brammer, who presented this information last week at the ACIP meeting. I have updated it with the most recent week's surveillance activity from our flu VE reports. For most of the surveillance systems I'm going to discuss, the data is current as of the end of surveillance week eight, which is the week ending February 22nd, 2020.

Moving to slide three, this slide summarizes

influenza virologic surveillance thus far for this season. These are results of influenza positive tests reported to CDC. We have two different main sources of this information. We have the clinical laboratories, which are shown in the chart on the left, and the public health laboratories in the chart on the right.

In either case, the calendar or surveillance week is on the X-axis. The left-sided Y-axis is the number of positive specimens for each virus type or subtype. And the Y-axis on the right is the percent of specimens that are positive. And that is designated in the clinical laboratory chart by the lines that you can see there.

So first looking at the clinical labs, in general, these specimens are not subtyped or subject to lineage determinations, so we have data for all A viruses, which are shown in yellow, and all B viruses, which are shown in green. You can see that, in the beginning of the season, there was a clear predominance of B viruses but that, in recent weeks, influenza A

viruses have predominated. You can also see on this chart, in the solid black line that represents the overall percent of specimens that were positive, this has dipped slightly in each of the last two weeks, although it's still rather elevated at above 25 percent.

For the public health laboratories, we generally do receive subtype and lineage data. For the B viruses, the Victoria lineage, in the lighter green, has predominated while, for the A viruses, H1N1 pdm09, in orange, has predominated. We're seeing relatively little in terms of H3N2, in yellow.

Moving on to slide four, outpatient visits for influenza-like illness, the left side shows percent of outpatient visits that were reported to be for ILI by calendar weeks. This is data that comes from ILINet, which is a network of providers who report weekly to CDC the percent of outpatient visits that they see for ILI or influenza-like illness. In the line chart on the left, this shows the current season in the red line

with the triangles and several earlier-selected seasons. We can see from the data that ILI activity in this network is still elevated, although there has been a slight decrease in each of the last two reported weeks.

The data that are reported to ILINet are also used to produce a map of ILI activity by state, so you can see a bit more of a geographic representation within the United States. This is what you can see on the right side of the slide. As of the end of week eight, we were still seeing substantial ILI activity with New York City, Puerto Rico, and 43 states reporting high activity and 5 states reporting moderate activity.

Moving on to the next slide, number five, this is laboratory-confirmed influenza-associated hospitalizations, data from the network FluSurv-NET thus far for this season. We have two charts here. The one on the left summarizes some cumulative data across all age groups by season. We have the 2011-'12

through the current 2019-'20 season here on this chart. '19-'20 is the red line that is sort of centrally located amongst all the other lines.

As of the end of surveillance week eight, the cumulative rate overall for all age groups was 52.7 per 100,000 population, which is similar to many of the recent previous seasons for this time of year and is substantially less than the relatively severe 2017-'18 season, which you can see on the line that soars up to the top of the slide. However, one thing to point out here, rates among school-age children and young adults are generally elevated compared to this time of year in recent seasons. Just looking at the chart on the right, which breaks things down by age group, the cumulative rate among children zero through four years old, the youngest kids, was 80.1 per 100,000 and is currently the highest CDC has on record for this point in the season, having surpassed rates reported during the second wave of the 2009 H1N1 pandemic.

The next slide should be influenza-associated

mortality. We have two charts again here. The first is from the National Center for Health Statistics mortality surveillance data. You can see a number of peaks here because, again, this slide, like many of our slides, represents a number of seasons. The current '19-'20 season is the one furthest off to the right.

In this data as of -- and this data is a bit -- approximately a week behind the other surveillance system data. This is data that has been confirmed as of the week ending February 27th and is for reports ending February 15th or received as of February 15th, 2020, which was actually calendar week seven rather than eight as most of the other data is. As of that date, 6.9 percent of deaths were reported to be due to pneumonia and influenza. This is below the epidemic threshold for week seven. The epidemic threshold is depicted by the black lines on the graph.

On the right, we have pediatric deaths associated with laboratory-confirmed influenza, which has been reportable for children under 18 years of age

since 2004. This slide too represents several seasons. In this case it's from '16-'17 through the current 2019-'20 season. Thus far for the 2019-'20 season, we have a total of 125 influenza-associated pediatric deaths that have been reported.

These include 87 associated with influenza B viruses, 18 of which were subject to lineage determination. And all were determined to be B/Victoria viruses. Then we also had 38 associated with influenza A viruses. 23 of these were subtyped, of which 22 were H1N1 pdm09 and one was an H3 virus.

The next slide should be entitled "Characterization of U.S. Influenza A (H1N1) pdm09 Viruses Collected September 29th to Present." And we're going to start with -- basically this slide and the three that follow are going to be antigenic and genetic characterization. So starting with the H1N1 pdm09s, all 606 influenza A H1N1 pdm09 virus that were tested belong to the genetic group 6B1A. All 74 of these viruses that were antigenically characterized

using a hemagglutinin inhibition assay with ferret antisera were similar to the cell culture propagated A/Brisbane/02/2018-like reference virus, which was represented in the 2019-'20 northern hemisphere vaccine.

Next slide, “Characterization of Influenza A H3N2 Viruses.” 386 of 406, or 95.1 percent, of A H3N2 viruses characterized belong to the 3C.2a1 subclade, 20, or 4.9 percent, to the 3C.3a subclade. 31 of 72, or 43.1 percent, of A H3N2 viruses antigenically characterized were well inhibited by ferret antisera raised against A/Kansas/14/2017 3C3a, the cell propagated reference virus representing the A H3N2 component in the '19-'20 vaccine.

Next slide for influenza B/Victoria lineage viruses, two genetic groups of B/Victoria lineage viruses are cocirculating, V1a1 and V1a3. 51 of 699, 7.3 percent, belong to V1a1 subclade, the remaining 648, or 92.7 percent, to the V1a3 subclade. B/Colorado 06/2017, the reference virus representing the

B/Victoria lineage virus in the '19-'20 northern hemisphere vaccine, belongs to V1a1 subclade. 83 of 131 or 63.4 percent of B/Victoria lineage viruses antigenically characterized were similar to the cell propagated B/Colorado 06/2017-like V1a1 reference virus.

Next slide, the last genetic and antigenic characterization slide for B/Yamagata lineage viruses, all 76 B/Yamagata lineage viruses tested belong to genetic group Y3. All ten B/Yamagata lineage viruses antigenically characterized are similar to the cell propagated B/Phuket/3073/2013-Y3, the reference vaccine virus representing the influenza B/Yamagata lineage component of the 2019-'20. And this for quadrivalent vaccines.

The next slide, just in summary for surveillance before we move to VE, influenza activity remains elevated, although there has been a little bit of drop in indices for ILI over the last two weeks. Influenza B/Victoria lineage viruses predominated early

in the season, but A H1N1 pdm09 viruses have increased in recent weeks. For the season as a whole overall, approximately equal numbers of B/Victoria and A H1N1 have been reported. Overall for the entire population, severity has been low, but hospitalization rates among children and young adults have been high. And thus far, 125 influenza-associated deaths in children have been reported.

Next slide. Moving to interim 2019-'20 U.S. VE estimates, these slides are courtesy of Dr. Brendan Flannery who presented this data at the February 2020 ACIP meeting last week. So the next slide, U.S. Flu VE Network sites and principal investigators, the Flu VE Network is a network of five collaborating sites that work with CDC. And we have those listed on this slide so you can see where they are along with their PIs.

Next slide, U.S. Flu VE Network methods, just a basic overview, enrollees are outpatients aged six months and over with acute respiratory illness with cough of seven or fewer days' duration. For these

interim results, the dates of enrollment are October 23rd, 2019, through January 25th, 2020. The design is a test negative design which involves comparing the vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls. Essentially all participants enrolled are presenting with acute respiratory illness, and they are sorted into cases or controls based on their testing results, RT-PCR positive or negative.

With regard to vaccination status, receipt of at least one dose of any 2019-'20 seasonal flu vaccine, according to medical records, immunization registries, or self-report characterizes a participant as having been vaccinated. VE is calculated as 1 minus the adjusted OR times 100 percent. The analyses presented here include adjustments for study site, age, sex, self-rated general health status, race or a Hispanic ethnicity, interval from onset of illness to enrollment, and calendar time.

The next slide moves on to our interim

results. A total of 4,112 participants were enrolled from October 23rd, 2019, through January 25th, 2020, at 52 clinics at the five sites. Among these, 1,060, or 26 percent, were RT-PCR positive, so these are our cases. 3,052, or 74 percent, were RT-PCR negative. These are our controls.

Looking at the viruses isolated from the 1,060 cases -- this is shown in the pie-chart -- we see a predominance not surprisingly of B/Victoria viruses in the light green at 59 percent, the next most common being H1N1 pdm09 in orange at 30 percent. Again, relatively little mirroring our surveillance data of H3N2 in red, not very commonly identified this season so far at about 1 percent.

The next slide should be interim vaccine effectiveness against medically-attended influenza A and B by age group for '19-'20. This is a table, and this shows all influenza A-B results without regard to type or subtype. We have overall results across all ages, and then we have some results that are broken

down by age group. Overall across all age groups, VE thus far was estimated as 45 percent with a confidence interval of 36 to 53 percent. Stratifying results by age group, we see statistically significant VE across all the age groups with some variability in point estimates, highest for children 6 months through 17 years at 55 percent and lowest for adults age 18 through 49 years at 25 percent.

The next slide, interim vaccine effectiveness against influenza B/Victoria by age group, wo this is a similar presentation but this time stratifying just for the B/Victoria viruses. The interim estimate of overall VE for B/Victoria across all age groups is 50 percent with a 95 percent confidence interval of 39 to 59 percent. Stratifying by age group, we had significant VE, statistically significant B VE, in both children 6 months through 17 years and adults. The adult category is collapsed here for 18 and older basically because of too small numbers if they're sub-stratified out further as they were done on the

previous slide. We do have somewhat higher of a point estimate of 56 percent among children as compared to the adults 18 and over at 32 percent.

Next slide, interim vaccine effectiveness for the H1N1 pdm09 viruses. Overall, we have across all age groups VE of 37 percent with a 95 percent CI of 19 to 52 percent. Breaking down by age group, we have statistically significant VE in the 6 months through 17 years age group and in the 50 and older age group at 51 and 58, respectively. We're not seeing statistically significant results yet for the 18 through 49-year-old age group. And this is something we'll be watching as the season progresses and we begin to see more results and finalize those.

The next slide. This is a pyramid graph: deaths, hospitalizations, and cases averted in the U.S. due to influenza vaccination. Over the last several seasons, CDC has provided estimates of influenza illness burden averted through vaccination. It's too early for the '19-'20 season estimates. Those are

expected in fall of 2020. We do have 2018-'19 estimates that were recently published. For the '18-'19 season, it's estimated that vaccine prevented approximately 4.4 million illnesses, approximately 58,000 hospitalizations, and approximately 3,500 influenza-related deaths.

The last slide is a summary slide. Interim results for the 2018-'19 season indicate vaccination reduced medically-attended illness due to any influenza virus type by about 45 percent based on enrollment through January 25th, 2020. We saw a higher VE in children overall at 55 percent against any influenza virus in that group 6 months through 17 years. Vaccination provided about a 50 percent protection against the predominant influenza B/Victoria virus, clade V1A3. Overall effectiveness against H1N1 pdm09 is 37 percent. H1N1 pdm09 (audio issues.)

DR. EL SAHLY: Lisa, are you still there? Lisa? So we're going to wait for them to call Lisa again. Is that what we're doing? Yeah? Okay. We'll

give it a minute. Hi, Lisa. Are you back on? Lisa? Is anyone else on, on the phone? Hi, Lisa. Are you back on? Lisa?

MS. HAYES: Lisa, we still can't hear you so we may still have the line muted. We're hoping to get it corrected shortly. Thanks for your patience.

OPERATOR: Phone check.

DR. EL SAHLY: Is someone on the phone? Is this Lisa?

OPERATOR: I don't hear anything.

DR. EL SAHLY: Is anyone else on the phone?

DR. GRUBER: We have a suggestion to make, I mean, since we already are at the summary slide. Perhaps we can just read that summary slide and then move on because, I mean, we had Lisa almost finishing the presentation. Because we don't really know when this IT problem gets fixed. We need to move on.

DR. EL SAHLY: Yeah. I was just telling Kathleen if we can potentially get the next presentation --

DR. GRUBER: Right.

DR. EL SAHLY: -- and then we can do Q and A for both.

DR. GRUBER: That's another good suggestion, yeah.

DR. EL SAHLY: Okay? All right. So hopefully with fewer glitches, Dr. David Wentworth, the Branch Chief of the Influenza Division, CDC, will do an overview of the global influenza virus surveillance and characterization.

GLOBAL INFLUENZA VIRUS SURVEILLANCE AND CHARACTERIZATION

DR. WENTWORTH: Excellent. Okay. Hopefully everyone can hear me. Can you hear me on the phone? I'm going to move to the second slide. This is me. And so we couldn't select influenza vaccines really without strong involvement of the global community and the global influenza surveillance and response system,

or GISRS. So year-round surveillance is conducted by GISRS laboratories, and these include the WHO collaborating centers; national influenza centers, abbreviated as NICs here; WHO essential regulatory laboratories, such as the FDA and TGA in Australia and IVSC in UK; WHO H5 reference laboratories.

So a consultation was held last week, the 24th to the 27th of February, where we review, analyze, and conclude based on all the data presented by all the WHO CCs, as well as other folks that are involved in the assessment of the viruses. So the nine advisors are shown here. This was chaired by Dr. John McCauley, who is individually shown over there next to the GISRS sign. One of the advisors, Dr. Dayan Wang, had to participate remotely because of the SARS coronavirus-2, COVID-19 outbreak. And 37 observers from NICs H5 reference laboratories, WHO CCs, ERLs, academics, the veterinary sector, OFFLU, and other government agencies participated.

The next slide. This is slide three for those

on the phone, the weekly number of specimens processed by GISRS. So 2019 is the black line there, and you can see our season worldwide started to pick up towards week 38, week 39, week 40, and then continued to increase and then begins as the red line for year 2020, right near the 140,000 mark there on the left-hand side of that slide. And it's good until week seven -- or six there.

This is the global picture of the circulation of influenza viruses. So Lisa gave you a nice overview of what's happening in the United States. I'm going to back up a little bit higher and try to show you the global -- what's going on globally.

And so the orange viruses in this bar chart are B viruses, and the blue viruses are A viruses. And so the darker orange is the Victoria lineage, and the lighter orange is the Yamagata lineage. And what you can see there, if you start going from the later parts of 2019, say, weeks 46 through 2020's week 7, the increase of viruses that are circulating, a mixture of

A and B worldwide, B/Victoria dominating in the B-lineage, and rather a good mix of H1 and H3 cocirculating with H1s a bit predominating in some areas.

This is an easier take of what was going on worldwide, this simple pie chart on slide five. This is the H1N1 was about 14 percent of the viruses, H3 about 15. So for the influenza A, they circulated about equal numbers globally. The number not subtyped is there, 30 percent, and then you can see for the B-lineage viruses there's very low Yamagata circulation. And most of it is B/Victoria lineage viruses with quite a few not determined, but we just consider the ratios to be the same in those not determined.

On slide six, this is the influenza activity worldwide, the H1N1 viruses now showing you by influenza transmission zone from September 2019 to February 2020. The light blue portions of the pie are H1N1 viruses, the darker blue portions are H3, and the very dark blue are not subtyped. And then again you

can see B are the orange parts of the pie. And so the take-home here really is there's geographic distribution of which viruses circulate in which zones and in which countries. You can see, for example, there were a lot of B viruses in South America and North America and fewer B viruses in South Africa. We'll drill into these numbers a little bit later.

Slide seven shows you the influenza viruses' sequence and made available through publicly accessible databases during just this -- since September 2019. These are primarily sequenced by the WHO CCs. So you can see thousands of H1N1s and H3s and B/Vics, and very few B/Yamagata viruses were even available to be characterized by genomics.

This slide illustrates the viruses genetic -- antigenically characterized over the past three northern hemisphere seasons. The light green is the current September 2019 to 2020 season. And you can see relatively equal numbers.

Now I'm going to switch to more details about

the specific subtypes and lineages. We'll start with the H1N1 pdm09 viruses on slide nine there. Slide ten, this is the number of H1N1 pdm09 viruses detected by GISRS during these 2019 and 2020 periods, our black and red lines respectively. And you can see that we're just -- it's just starting to be in a downturn now around week five there.

Slide 11 shows you the geographic distribution of the pdm09 viruses. And, as Lisa mentioned, we had a lot of those in North America and the United States, in particular. And you can see far fewer H1N1 by percent positive of the samples tested in other regions around the world where they saw more H3, for example, or B or both.

Now, I'm going to get into a bit about the phylogenetics and geography of the viruses and more particularly which clades and subclades are cocirculating. If you remember to the last VRBPAC meeting, we had a real wide array of different subclades of H1N1 pdm09 viruses. This is a

phylogenetic tree, a very large phylogenetic tree produced by our colleagues at the University of Cambridge, Derek Smith's group.

At the top of that tree are the older viruses and you can see that whole -- about halfway down, those are the viruses that were circulating previously. And so to the right of that tree is a heat map that is really a time -- each column represents a month. And so I've highlighted some of the months so that you can read them more clearly. So it starts on the left there, June 2018. Then it goes to January 2019, June 2019, and January 2020.

And so what you can see is that wide array of viruses have now collapsed down toward the bottom of the tree to these three main groups, the 6B1A-7 viruses, which are there at the top. You can see those are primarily circulating in South America and North America, hence the light blue and dark blue coloring of the dashes of the most recent viruses. We also have quite a few 6B1A-5B viruses. And these are again in

North America and South America, but there are some seen in Oceania as well.

And then by far the predominant group has really become the 6B.1A-5A viruses. And you can see how they're globally disseminated, and they make up a lot of the recent viruses. They really emerged starting in January of last year but have continued to spread and increase.

And within that 5A clade, subclade, there's a group of viruses that we're just demarcating right now as D187A and Q189E, and they're in the bottom of that phylogenetic tree. And so you can see there that they're the most recent viruses, and they make up a lot of the viruses towards the bottom there. And they're circulating globally, so Asia, Europe, North America, et cetera.

Slide 13 shows the recent residue changes on the molecular structure of the monomer of the hemagglutinin molecule. And so for your reference, on the left-hand side of that slide, the 6B.1A-5A virus is

shown compared to the current vaccine virus, the cell-based version of that which is Idaho/07. And it also is highlighting the major antigenic sites that have been defined for this H1 molecule. And so you can see antigenic site Sa is that kind of gold-colored site. Antigenic site Sb, these are the most predominant sites of the tip of the molecule is the blue site. And you can see how they border the RBS, which is the receptor-binding site. And then there's two other sites. These are a little bit more on the side of the molecule, antigenic site Cb and Ca and those are yellow and green, respectively.

And so we've marked what the amino acid substitutions here in the 5A group are. They're the T185I, the N129D, and the N260D. And then that newer group of virus that has recently emerged and become predominant worldwide are these 5A viruses with the additional 187A and 189E. And so there you can see how they could be impacting that site Sb all up there when you think about it. The previous vaccine change was

changed in part because of a substitution at 183. So over the past five years or so, we've seen the evolution of the virus in this site going 183, 185, 187, and 189, all being changed.

Now, when we analyze these viruses using ferret antisera for reactivity against the A/Brisbane/02-like viruses, here I'm showing you the antisera to the egg isolate of Brisbane/02, so very similar to the vaccine strain for the egg viruses. You can see 93 percent of them are considered like the vaccine virus and 7 percent of them are considered low. And those 7 percent typically have a substitution in the 153 to 157 corridor of amino acids which in site Sa.

This next slide on slide 15 shows antigenic cartography of HI data using the ferret antisera. And on the left-hand side of that the cartography is based on hemagglutination intervention data from the CC in Atlanta since 2009, so you can see the dissemination of all these viruses that we've identified. The

Brisbane/02 egg is shown as the dark blue large circle and the Hawaii/70 cell and Guangdong-Maonan/SWL1536 egg shown right there as well.

What you see far away from that are the positions that have come up in the past three years or so, 156D, 156K. So 156N is the original blue dots, whereas the D and K are represented by the orange -- or the yellow and the orange dots, respectively. And so that's the thing. The ferret can really hone in on that site Sa quite well and really discern those antigenically.

Now when we do antigenic analysis with human and ferret sera for comparisons here on this slide -- this is slide 16. I'll walk you through this because it's -- I know it's an HI table, and they're not that fun. But on the strain on the reference viruses on the left-hand side, we have past vaccine viruses, California/07, the early H1N1 pdm09 vaccine, Michigan/45, the 6V.1 clade HA that was changed to a new vaccine and then Idaho/07, the one that was most

recently changed. This is a cell version of the Brisbane/02 virus -- and a Maine/38, which is a virus that has the 156K substitution but that emerged last year, so it's not in the P5A clade. It's in the P2 clade, but it still has that substitution.

So ferret antisera against Idaho/07, you can just cast your eye down that column, and the only place you'll see it drop titer significantly from the 2560 is when there's a 156K virus. So you can see that Maine/38 at the top drops to 160 and the Wisconsin/588 from 2019, which is now a 5A that's evolved to 156K substitution, has dropped to 160. But all the other groups, the major circulating groups that we've tested aren't recognized as different. And the reciprocal is a little true with the Maine/38 antisera.

Now, let's turn your attention to the human adult sera. So these are just post-vaccinated adults individually looked at. And here we have two adults from the 2010-'11 vaccination campaign, and their homologous titer would be to California/07-like virus

is 1280. And you can see how it drops to 320 for this individual, number one, against Michigan/45 and then stays around there, actually jumps up with the Maine/38 with the 156K. And it's a little bit more cross-reactive with that virus, quite contrasting the ferrets. And if you look at the second individual, there at 2560. They seem to be cross-protected against many of these viruses.

Now the next two individuals were vaccinated with Michigan/45-like virus, and the first one is a homologous titer of 1280. That drops to 640 for most of the next viruses down. But then, when you get to the Nebraska/14 -- this is the group with the 5A plus 187, and 189 -- and you can see it drops further to 320 and doesn't drop any differently to the 5A with the 156K, quite contrasting the ferrets.

And then Michigan/45, the last individual, has a homologous titer of 320, and they drop to about 80 with the vaccine from last year, the Idaho/07, again, don't change from that with the 156K substitution, have

80 with the 5A virus but then drop again to 40 with the 5A that had the 187 to 189E. And it's very similar with the 156K virus. They also react poorly with the 5B viruses and some of the 7, the subclade 7 viruses.

Okay, so now I'm going to go to human serology. Now these are individuals vaccinated with last year's vaccine, the 2019-'20 vaccine. And here we're looking at the post-vaccination hemagglutination, inhibition titers for the geometric mean titers relative to the cell propagated Idaho/07.

And so you can see the vaccine covers these Idaho/07-like viruses very well. And then we have representative viruses across the top here. So that's the antigen they were tested against is on the top there. So for example a 5A virus is a Nebraska/15. A 5A with the 187 and 189 is the Nebraska/14, and a 5B is the Maryland/42.

And then we had 12 panels of human sera that were tested. So we're trying to test a lot of human sera. Typically, the pediatric sera gives us the most

sensitive window for antigenic drift of the virus, and you can see that here. They're the first row. There are 6- to 35-month-old pediatric sera. You can see some reductions to the 5A and the 5B viruses. And then the next two sera are three to eight-year-old pediatrics. And both egg vaccine and cell vaccine are being compared there in the top row and the next row down.

I'm not going to walk you through the entire table. I think the easiest thing to do is -- the reason we've color-coded it is because green is good. Dark red is significantly low. And as you move from light orange to darker orange to the red, that's where you're getting reduced reactivity patterns. And so you can kind of look at this, at the different age groups and the panels from USA versus UK, Japan, et cetera. You can see some of the ones that are low are in the 5A, 187A, 189E, as well as the 5B, which is consistently low but really currently only circulating in North America.

Now, this is the same human serology compared against the egg-propagated Brisbane. And that will just kind of accentuate the differences. And you can see that we see more orange and reds with that.

So to summarize the H1N1s, the pdm09 viruses predominated in some parts of Europe, North America, Asia, and Africa. HA gene sequences belong to clade 6B.1A, with subclades 5A, 5B, and 7 all cocirculating. The majority of the viruses now belong to the subclade 5A, which has four amino acid substitutions characterizing that group, which is N129D, S183P, T185I, and N260D. And then most 5A subclade HA proteins also have evolved D187A and Q189E substitutions in this site Sb. We've also seen a recent emergence of 5A subclade that has acquired the N156K substitution in site Sa, which we will be watching closely. Ferret antisera raised against the pdm09 virus, Brisbane-like viruses, Brisbane/02-like viruses, well recognized circulating viruses with the exception of those that have substitutions in 155 or

156.

Now I'm on slide 20. The summary, two human post-vaccination antisera showed reduced inhibition of viruses that express recent HA subclades such as the 6B.1A 5A with the 187A and 189E, as well as the 156K viruses. Sera collected from humans vaccinated with the 2019-2020 vaccines had reduced geometric mean HI titers to clade 5A 187 and Q189E substitutions, and 5B viruses had reductions compared to the Brisbane/02-like viruses.

Okay. So I'm going to turn our attention now to the H3 viruses, H3N2 viruses. I'm on slide 22. The number of H3N2 viruses detected by GISRS are shown on this slide. You can see it really started to peak up towards the end of 2019, beginning around week 44-45 and now is on the decline as we enter week 5 on this graph.

This is the geographic distribution of the H3 viruses. If you remember back to the -- this is the number of percent positive in these different locations

around the world. You can see there are quite a few in Asia and Europe and parts of Africa.

Slide 24 is the summary of reactivity of H3N2 viruses using neutralization assays. So you can see the grand total of about 40 percent are considered like the Kansas/14 2017 cell. Remember that's in the current vaccine that was used. And 60 percent are considered low.

Remember the geographic distribution of the viruses is in different places. And so you'll notice that some WHO CCs have quite different numbers than others. And these sometimes are in part to different viruses -- different types of viruses circulating in the regions where they obtain the viruses from.

Now, slide 25 shows the reactivity pattern against the Kansas egg virus. And there you see that it pushes more of them to a higher fold reduction, so we end up with more in the eightfold low category, about 88 percent total. Slide 26 is now showing you a phylogenetic tree, again, a very large one.

And I'll go through this a little bit. We have at the top of that tree the 3A viruses. This is the clade that the Kansas/14/2017 vaccine strain is in currently. And you can see how predominant that was in North America from January through June 2019 there and how it emerged a little bit in Europe. And now you can see in January and earlier December, November, really it dominated the European season, the 3A-like viruses that were in the vaccine.

Below that are the 2A2 viruses that caused our big season 2018-2017 timeframe. And then further below that are where a lot of the 2A1b viruses are currently that are cocirculating. We have a group that have a 135K substitution. They originally evolved around mid-2018 and are globally disseminated. Then we have a newer group of viruses, the 135K with 137F, 138S, and 193S. I'll typically refer to these just in the shorthand of 137F viruses to try to make it a little cleaner when I speak.

So these originally emerged in Asia about this

time last year and now are started to disseminate globally as you can see by the color coding, the red dashes and then it turns to blue and green and some pink even. And then the 131K viruses, these are like the South Australia/34 vaccine virus that was nominated for the 2020 southern hemisphere vaccine campaign. And you can see there at the bottom of that tree, they emerged quite a long time ago and have continued to disseminate and evolve a few amino acid substitutions within their groups and subgroups. So a lot going on with the H3s, as usual, and multiple cocirculating subclades that are antigenically distinguishable.

This slide tries to put it graphically which clades and subclades are cocirculating. So these pie charts that may be a little small for individual countries may be a little hard to see, but the main point is there's different clades and subclades circulating in different regions of the world. And that makes, of course, choosing a vaccine very difficult for the whole northern hemisphere.

So you have the 131K viruses are the yellow viruses. They're a little bit kind of older. They've been around for a very long time, the yellow pies -- or pieces of pie. Then the orange ones are the 135K viruses. And you can see how they're really in Africa quite a bit. The 3C3a viruses are represented by that red color, you can see in South America, Central America, and Europe and then this newer group of the 135K plus the 137F, et cetera, really circulating in Asia but then starting to disseminate globally westward.

Now I'm showing you a molecule here. This is again just like the H1. It's a crystal structure of the monomer of the HA. There HA is actually a trimer of these, but it's a little bit easier to focus on the monomer. Now, the antigen excites are labeled in the color coding there. And Iowa/60 is a base 131K virus and the recommended cell vaccine candidate for the southern hemisphere 2020.

And so the 2A1b, 135K, 137F group is shown on

the right and where those substitutions are. You can again see up in the head where's there a lot of antigenic pressure. There's a substitution at 137F that kind of defines that in terminology, 138S and 193S. 193S is actually a substitution that also evolved in the 3A viruses that allowed them to take off. And then we have T128A, as well, on the other side when you rotate it 180 degrees.

This slide 29 shows the antigenic cartography of the H3N2 viruses now. The green dots are 3C3a viruses, and so here it's much easier with ferret antisera and virus neutralization tests. Remember, we can't really HI effectively the H3N2 as much as we used to be able to, so we depend a lot on virus neutralization type tests. So here we're looking at cartography using virus neutralization tests. And you can see those 3A viruses in the Crick data on the left and the CC Atlanta data on the right. And they're pretty consistent. When you can do an HI well, it still works.

So you have the 3A viruses are green. The kind of purplish-blue are 131K viruses. You can see how they dominate in some regions. And the red-colored dots are 135K viruses. And so you're seeing some overlap in all the 2A1b viruses, and this has been true. Where we're releasing the most distinguished viruses are in the 135K plus the 137F, 138S, and 193, which are the pink viruses.

This shows you a hemagglutination inhibition. I'm on slide 30 now -- I mean, a focused reduction assay from the CC in Atlanta. The top reference virus there, number one is Iowa/60. That's the cell prototype 131K vaccine for the 2020 southern hemisphere. And you can see it has a pretty high homologous titer of 5120. It covers many of the viruses that are circulating pretty well.

If they're 131K, you can see how well it does, but it starts to drop coverage with the 135K, 137F group. And also we have seen, in general, some reductions of some of the other distinguished groups,

particularly this 135K, 186D group that's towards the bottom. It's the virus from Togo/1307 and Ohio/30. Those are representative of that. And then you can see how poorly they cross-neutralize the 3A viruses. And then going to the far-right side of that column, you can actually see how well the Kansas/14 cross-neutralizes and cross-protects against some of these other cocirculating groups, even though ferrets can antigenically distinguish in a unidirectional way. So they are fourfold, sometimes eightfold down, but it is showing some cross-neutralization.

Now, we've included some antisera here to this new group, the 135K, 137F viruses represented by that Hong Kong/45 in an egg cultivar which is Hong Kong/2671. And so you can see the sera to both of those viruses and the antigens. So those are antigens three and four, and you can see how well the sera against that virus covers most of the circulating groups, not only its own group but does pretty well against the 131K viruses and only lacks coverage of the

3A viruses.

Now, I'm turning to slide 31. This is analysis of post-vaccination sera. Remember, humans were vaccinated in the 2019-2020 season with Kansas/14-like virus, and so that's what you're seeing in the first column here is reactivity with a Kansas/14 cell antigen. And then, I have all the different vaccines that were used, our IIV4 vaccines, Flucelvax. Row ten is Flublok, sera from Flublok provided by CBER FDA. And so you can see all those vaccines in all these different age groups did pretty well against 3A viruses and covered those very well. Where you can see huge antigenic distinction is typically in the young, and that's true here.

The 6- to 35-month-old pediatric in row one, you can see that virtually all the currently circulating groups that we're nervous about, 131K plus additional substitutions -- and the very last column is this 135K with the 137F, et cetera, represented by the Hong Kong/45 antigen. And that one is consistently low

across the board. And it's more pronounced when we compare it to the egg virus.

This is on slide 32 now. You can see kind of the shift from green to orange to red as you kind of go across that group. I'm not going to waste your time by walking through each serum, but there's a lot to be learned from the human sera. And it's very complicated because of people's prior exposure history. The cleanest sera, of course, is the pediatric population.

If we go to slide 33, this is the first summary slide for H3N2s, 3C.3a, and 2A1b viruses co-circulated widely with regional heterogeneity. The 3A circulated primarily in Europe and South America. 2A1b, 131K continue to circulate. These have been around for a while now. The 2A1b with the 135K has now divided into two subgroups that have additional substitutions.

The one I spent more time on is this one that's more common right now is the 137F, 138S, and 193S, substitutions that's widely disseminated

throughout Asia, has been there for almost a -- quite a long time now, and found in Europe, North America. The S198P group that has a number of other substitutions primarily circulated in Africa and sporadically in other regions. And so it's a little bit newer emerging subclade within the 135K group.

Slide 34 is a second summary, the antigenic characteristics. The ferret antisera to 3C3a-expressing viruses were antigenically similar to each other, so all currently circulating 3As really look antigenically like the vaccine virus. But they showed reduced inhibition of 2A1b HA clade viruses.

When we take sera to 2A1b HA clade viruses, this shows poor neutralization of 3C3a viruses, so there's clear 2A antigenic distinction between those two groups. And some of the subgroups within the 2A1b were antigenically distinguishable, but overall 2A1b viruses do cross-react with each other. The most pronounced titer reductions were seen in the 2A1b-135K, 137F, 138S, and 193S substitution group.

The 2A1b-135K plus 137F, et cetera, viruses did inhibit the 131K viruses fairly well, but the converse was not observed. Okay. So the sera against the 131K doesn't do as good a job cross-neutralizing the 137F group as the sera against the 137F group does against the 131K viruses.

Human serology studies using serum panels from people vaccinated with Kansas/14/2017 3A viruses, recently circulating clade 3A viruses were very well neutralized. GMT titers against representative viruses from the genetic group 2A1b were reduced. This was most notable in sera obtained from the very young children, 6- to 35-month-old. The 2A1b-135K, 137F, 138S, and 193S viruses such as the Hong Kong/45/2019-like virus had reduced GMTs.

Now, I'm going to change your attention to the other main group of viruses, influenza B viruses, and we'll start with the B/Victoria viruses. This is now showing -- slide 37 is showing the activity from September 2019 to 2020. As you heard from Dr.

Grohskopf, we had a lot of influenza B activity in the United States and in North America in general. You can see in South America and then parts of Europe and Asia and Africa.

This is the number of B viruses detected by GISRS overall, and you can see how low it was in previous seasons such as 2017 and 2018 being a big season and then nothing the following year. And then as you get into 2019, you see this rapid emergence of these viruses and really going to dominance and continuing to increase as you get into 2020, where the black line becomes the red line. This slide, number 39, shows the lineage distribution. And I mentioned this earlier, but really you can see, in most areas around the world, it's a real dominance of the B/Victoria lineage viruses, the one exception being South America where there was quite a bit of B/Yamagata circulation as a group.

So to get into the characteristics of B/Victoria lineage viruses, this is showing the HA

clade diversity based on sequence availability. If you remember, the Brisbane/60, the old vaccine strain prior to the Colorado/06 change which was fairly recent, was a V1A virus, so that would be the green bar. There's still very few of those circulating, some in Asia.

The V1A.1, these are viruses that acquired two deletions in the hemagglutinin gene, and they really dominated our seasons previous -- the past couple of seasons. And this is the group where the vaccine virus is in. And then the V1A.3, which really emerged January, February last year and then rapidly swept across the world is shown in the blue bars.

Slide 42 kind of shows you this. Okay? So there's really -- you can see the phylogenetic tree on the left, the color coding for the locations on the far left, and the top of that tree, really the viruses circulating in January 2018, primarily the old V1A viruses at the very top. We had the emergence of a triple deletion called V1A.2 very early on, but you can see it's -- it just kind of died out. So that has the

same amino acids deleted as the current triple deletion, which is the very bottom of the tree. So different mutations had to occur to allow that to be a successful virus.

Then a little below that, you can see the V1A.1 viruses, which really started to increase in January 2018, really identified in South America and North America, and then swept worldwide as we moved into 2020. And then you can see where these V1A.3, which also have the 162 to 164 deletion, really arose last year about this time. Actually at the time of VCM, we really don't have the sequence data where you can see January 2019 because it takes a month or two before sequence data gets deposited in the database. And so you can see how rapidly it emerged and started out in one part of the world and then swept into our parts of the world by the time fall came. And so the majority of the viruses, as you heard Lisa say, that affected our population this year are these V1A.3 viruses.

This shows you the reactivity pattern with the V1A.1, B/Colorado/06-like viruses with all the viruses that are cocirculating. Remember, most of these are V1A.3 viruses that are tested, so it's -- the antisera to the V1A.1 viruses is cross-reacting with some of those to a certain extent, particularly with the cell virus. This of course gets worse when you use the egg virus and make antisera to that. It doesn't cross-neutralize so many of the V1A.3 viruses using ferrets as a model.

Now, when we look at the reactivity against Washington/02, this is the recommended vaccine for the southern hemisphere in 2020. This is a V1A.3 virus. You can see that 87 percent of them are covered with the cell version, and 89 percent are covered by the egg version of the virus.

Slide 45 shows you the antigenic cartography. Again, looking at the various viruses, the vaccine viruses are the large circles, and the test viruses are the small circles. You can see how the gray viruses

represent older viruses that are older than six months old. And so you can see that most of the viruses now circulating are really these three deletion viruses, which are the V1A.3 viruses. And where the Washington egg and Washington cell sit in that cluster, you can kind of draw a circle around those, and they'd be covering most everything in that circle.

Slide 46 walks you through an HI. Again, the highlighted column shows Iowa/06. This is a cell version of a vaccine virus that was used, the V1A.1 double-deletion virus. It's known as Iowa/06. It has a homologous titer of 320. And you can see it drops a little bit, four to eightfold typically with viruses in the V1A.3 group but does show some cross-reactivity. And it does show good cross-reactivity again with viruses that are older, the V1A viruses. And so that was kind of in the middle of this evolution. Then if you get to the Washington/02 viruses -- these are the V1A.3 -- the sera is shown there under that darker blue, V1A.3. We have the egg and the cell, and you can

see the 320 homologous titer does very poorly against the V1A virus and the V1A.1 viruses but does very well protecting against all the V1A.3 viruses that are circulating right now.

This is analyzing human post-infection sera. Remember they were vaccinated with Colorado-like viruses which are V1A.1. Does a very good job against those viruses. They're all green. Actually cross-protects pretty well in this type of analysis with V1A.3 viruses, and the most unique virus we could find is this V1A.3 with some additional substitutions -- this is a pretty rare virus -- is also neutralized. One of the difficulties here is the homologous titer of the test antigen, Iowa/06, was quite low, so it doesn't give you as nice resolving power as we like to have.

When we compare to the egg-propagated reference, now we can get a higher cross-titer with the Colorado/06, so it gives you a little more resolving power. But you do see some reductions against even the

cell counterpart, the Iowa/06, and then similar reductions against the Washington/02. And it actually looks better against the Washington/02 egg than it does against the Washington/02 cell, which is consistent with some of the egg epitopes generating immunity to that.

Okay. So to summarize the B/Victoria lineage, the phylogenetics of the HA, it's actually pretty simple right now. The majority of things circulating are V1A.3 viruses. They have this triple deletion in the HA, 162 to 164. There's a minority circulating of the V1A.1, which has the two amino acid deletion in the same exact region of the HA.

Antigenic analysis with ferret antisera shows that the Colorado/06-like cell virus inhibited V1A.1 clade viruses well but did show some reduced inhibition of V1A.3 viruses. The ferret antisera to B/Washington/02 viruses, which is a V1A.3, well inhibited its own clade viruses but very poorly inhibited V1A.1 and V1A viruses. And then human

serological analysis showed limited cross reactivity when compared to the GMTs of cell reference viruses, but the cell reference had a low GMT to start with. That's a little bit of a caveat there. And then they also showed reductions when compared to GMT of egg viruses.

Finally, I'll change to the B/Yamagata lineage viruses. Again, we'll start with a phylogenetic tree and the phylogeography. You can see, back in January 2018, there were quite a few B/Yamagata viruses cocirculating in these various regions, but it's a pretty what we call flat tree. There's not a lot of evolution in that tree. They just seem pretty successful.

And then they went through a crunch, and now really we only have viruses circulating primarily in South America, as I mentioned earlier. And you can see that's the group kind of in the middle there, the light blue dashes. But they don't have huge reasons like amino acid changes to make them more fit. They look

pretty similar.

Slide 52 shows reactivity of antisera against the vaccine viruses, B/Phuket/3073, the cell-like virus. You can see 90 percent of the viruses that we're able to test are considered like and 10 percent considered low. And when we compare against the egg virus, this drops a little, and you have 30 percent like and 67 percent low.

Slide 53 shows antigenic characterization of the B/Yamagata viruses. You can really see the MDCK version of Phuket covers all the viruses that are the test viruses that are circulating here from various regions around the world. Here we have a lot of viruses from Pakistan, Haiti, Laos, et cetera, but this is true of the very few we can find in the U.S., for example, antigen number 11, North Carolina/05 there. We do see some reductions with the antisera produced against the egg cultivar of B/Phuket.

But human post-infection vaccination sera tested here. We didn't test as many panels against the

very few viruses that we think may have some antigenic changes, such as these Y3 with a 230N or a Y3 with a 233N. You can see there that the 233N appears to have a more significant impact with human antisera generated against B/Phuket viruses, and that's showing you compared against the cell virus on top and compared against the egg virus on the bottom.

So to summarize the Yamagata, we have very limited circulation. It's primarily in South America. The phylogenetic shows that all of them are in clade 3. Antigenically, they're similar to the cell culture propagated B/Phuket/3073/2013 virus. We saw some reduced inhibition by ferret antiserum to the egg propagated cultivar of that virus. Post-infection human sera well inhibited representative circulating viruses well when comparing the GMTs to cell propagated virus. Reductions were seen in some panels when compared to the egg-propagated virus.

And so I don't need to go through this next slide because we started there with the

recommendations. Maybe I'll leave it there for a second to remind you, but I think it's in your booklets. The Guangdong and Hong Kong represent changes from the southern hemisphere. The Guangdong, Hong Kong, and Washington viruses represent change from the last northern hemisphere recommendation.

And then to acknowledge all the WHO collaborating centers in Beijing, Melbourne, London, Tokyo, as well as WHO Geneva staff, all of our GISRS partners at the National Influenza Centers, our University of Cambridge partners who did the cartography and some of those large phylogenetic trees, the ERLs, U.S. partners such as the Association of Public Health laboratories, United States Air Force School of Aerospace Medicine, Naval Health Research Center, our fitness forecasting partners which I didn't show you much of their data in Europe and U.S., and of course all of our CDC staff with a special thanks to Becky Kondor, Summer Galloway, Min Levine, and Xiyan Xu. Thanks.

DR. EL SAHLY: Thank you, Dr. Wentworth. Lisa, are you back on the line? Dr. Grohskopf?

CAPT. GROHSKOPF: Hello. I'm here.

DR. EL SAHLY: All right. So we have our two speakers available to answer questions from the committee. So Lisa, because of the technical difficulties, we decided to combine the Q&A to you and to David at the same time.

I guess I'll begin with a clarifying question. So for the B/Victoria post-vaccination human sera, when you test those sera against a cell-propagated Victoria, you will not identify differences. Only when you use an egg-grown, you will identify those differences, and what does it tell about the test itself, really?

DR. WENTWORTH: Yeah, yeah. So that's why I put the caveat in, and I appreciate you giving me the opportunity to explain it a little bit better. So really what happened is there's a very low homologous titer with the cell virus, and that's just by the biological nature of the virus. And so what that does

to us is it does allow you still to see antigenic difference, but it decreases the resolving power. So once you get down below a certain titer, it's hard to see, you know, the meaningfulness of the assay. Our titer will stop at say five.

DR. EL SAHLY: Okay.

DR. WENTWORTH: So you're going from a titer of say, for example, 80 or 40 to 5. So you have that resolving power. And it's just nicer when you have the resolving power, say, at, you know, 160 or 320 or something like that because we can still go all the way down to 5. So you can discern the antigenic difference farther. But if there was a big antigenic difference, you'd be able to see it with the way we did it because a 40 to 5 is a very significant difference, for example.

So we're seeing cross-protection. It's just that it would be nicer if it was a little bit higher. The previous VCM, we had a little bit higher titer, and we saw similar cross-protection.

DR. EL SAHLY: So there was cross-protection with the triple deletion?

DR. WENTWORTH: Yeah.

DR. EL SAHLY: It's just that -- okay.

DR. WENTWORTH: With human sera --

DR. EL SAHLY: With human sera.

DR. WENTWORTH: -- it gets reduced with that pediatric population that really hasn't had prior exposure by infection or vaccination.

DR. EL SAHLY: Okay. Okay. Dr. Spearman?

DR. SPEARMAN: Hi, I have kind of a big picture question for both of our speakers or either one who could take this on. So looking at the phylogenetic analysis and the antigenic analysis and the serologic analysis from vaccines, how can we relate that to what we're seeing currently with the interim vaccine effectiveness? For instance, if we just think of the H1N1 right now, there's -- in the adults it looks like the effectiveness is not there.

And yet, I didn't see a big mismatch or a big

lack of match serologically in what was presented for the H1N1. So can that be -- am I missing something? Can that be explained by antigenic drift, or is this something completely different?

CAPT. GROHSKOPF: This is Lisa. Just some thoughts on that from the perspective of the Flu VE Network, one thing in that system at this point is that in the adult age group they've been seeing more H1s than Bs, particularly recently. The numbers are currently smaller for H1N1s. We may see a difference in the VE as the season wears on and we begin to see more in that age group. Of note, the interim estimates from our understanding in Canada within a similar age group of 20 to 64 years were somewhat lower than they became later, probably as a result of the increasing numbers and greater precision of estimates.

DR. WENTWORTH: Okay. So I -- and I think I'll just -- I'll touch upon it too because I don't think you're missing anything there. It's a bit confusing. I do think these are interim VEs, so that

could impact it. And I think that the human sera really shows pretty good neutralization in that age group. So there is some inconsistency there.

Remember, VE is an estimate and not some mathematical model, and there's a lot of -- you know, you have to go seek healthcare as one of the ways to be tested. So there's factors there that are involved. I think the more direct evidence that it cross-protects is in the human sera, but of course it's a little bit of hand-waving.

We're not seeing that kind of huge antigenic distinction there. You can see what I showed you with human sera. Some people cross-react very well. Others are showing reductions. And the main reason I show that is to illustrate that these very dominant sweeps of amino acid changes are having an antigenic impact. It's not to say that the vaccine's poor or good.

It's really just to illustrate that do these changes impact the structure of the protein when ferrets aren't recognizing that change. And the fact

that some humans recognize that change do say that it's changing the structure of the protein.

DR. EL SAHLY: Dr. Offit?

DR. OFFIT: Yes. Question for you, Dave. So I just -- two years ago we picked for our vaccine strain -- for the H3N2 we picked a 3C2a clade. It ended up being, at least at the end of the season, a 3C3a, which dramatically reduced efficacy.

This past year in many ways the opposite was true. Right? We picked up a 3C3a clade. It was mostly 3C2. And then for the B/Victoria, we picked a V1A1. It ended up being mostly V1A3.

I mean, as you said early on, flu is a moving target. It's really hard to predict. But if you go back to the data that we had in March when we were making those picks, is there anything in those data now that you knew what happened, that would tell you, you know, maybe this was a clue that we could have gone with a different clade than the one we went to?

DR. WENTWORTH: Yeah. It's really important

to almost be an armchair quarterback for yourself and really look back and see. And it's partly why I pointed out that emergence of the B virus, that triple deletion mutant. We saw very few of those at this time last year. And when you think about it in protein space, they're exactly the same as the ones that had just died out.

So really, I mean, I could look at it now and say, well, there's something to think about, but we just started putting things in eggs. You know, we wouldn't have had Washington/02 had we not at least thought about doing something with those, so we did start putting things in eggs so that we had them available for the southern hemisphere selection.

But there's just very few data. So it's kind like the Yamagata right now. I can't see making a different choice at this time last year, personally, on the B Vics. And I think the human serology data at this time last year also told you that we did have a few of those strange viruses in our serum tests, and we

did see some neutralization of those viruses by kind of that broader immune response that most humans have versus a ferret, you know, which is a very naïve model specifically designed to pick up single amino acid substitutions. Right.

DR. EL SAHLY: I think also last year was more double deletion than triple deletion.

DR. WENTWORTH: Far more. Even --

DR. EL SAHLY: Yeah. So that was the --

DR. WENTWORTH: And the trajectory of those, like when you looked at the fitness forecasting models, was very high. There wasn't enough data to say that this V1A.3 virus could sweep the world in about six months' time. It was very unusual for an influenza B virus to move that rapidly. But with regard to the H3, to answer that question, I think that one was a much harder decision, and one of the drivers of that decision was how antigenically distinct the 3C3A viruses are. As I mentioned, we've been dealing as a human population, particularly in North America, with

3C2A viruses since 2014.

So if you look at our human sera over all these years, we've had many exposures to 2A1 viruses, both by vaccination with Hong Kong/4801, Singapore, North Carolina in the cell. Right? And so we had that. And then if you think of the 2A2 viruses, that was the one that caused that huge, really severe season that we've discussed a couple of times. That is also a -- it's a 2A virus, and it actually is 2A1-like in that it also has 131K.

So even though we defined that group as 131K, the 2A2 viruses that caused that really large season and infected a real big chunk of our susceptibles had a 131K. So in part, what we did last time was look at that Kansas/3A virus and see that it was really low in the human serology, very antigenically distinct using ferret antisera. And we went with the one that was the most distinct because that would have the greatest impact on people that already have prior exposure.

Where it can be a huge misstep is in the

pediatric population, which is so important, you know. And that's where picking the perfect strain, I think, is the most important. But that's where it's very difficult. But you can -- I'll just finally say that there's something about the 3C3A Kansas virus that does induce a lot of immunity that does work against the 2A1 viruses.

DR. OFFIT: Is that because it's sort of originally antigenic, in a sense?

DR. WENTWORTH: Yeah. I think it's a combination of just -- I would just call it memory. As I mentioned, we've been dealing with 2A1 viruses since 2014. Some of it may be OAS, but some of it may just be repeated exposure vaccination to those viruses. And then when you hit them with something -- you hit all of us with something very new, the Kansas, it might stimulate quite a bit of memory there and then really only induce a primary response to the different pieces that are Kansas-like. It's getting very hand-wavy. Yeah. But…

DR. EL SAHLY: Dr. Bennink?

DR. BENNINK: Yeah. Two quick questions. The first one is on where you were talking about the B viruses. Did you consider anything about the Phuket in terms of the egg-grown virus because that titer's going down, anything different --

DR. WENTWORTH: Yeah.

DR. BENNINK: -- to improve it?

DR. WENTWORTH: We're looking very closely at that. You might have noticed in our table, we have a couple of new Phuket viruses, one a French Guiana virus, and I can't remember the other one. But both of them do have a little bit better egg properties but not so substantially to warrant, you know, changing to that, particularly when we don't know which way the Phuket is going.

Obviously, it's under a lot of pressure being so low across the entire globe. It may be in part due to the wide sweeping of the Victoria viruses really impacting the niche for that virus, I don't know. But

it's hard to choose something different. Updating the Phuket could be a possibility if it continues to -- if the egg continues to decline. Maybe updating in part just because it would be a better egg virus may be a good idea.

But it's very difficult if you update and then the virus goes a different direction. We see some very strange, you know -- of the very few Yamagata viruses that are out there, there's some very strange ones that have six mutations and really only cross-react with highly polyclonal sera. But they're so few and far between you can't pick them other than to maybe make an egg virus or something like that.

DR. BENNINK: And the second question is to go back to the H1N1. Do you have any -- and this is just Phuket. Do you have any preliminary data or anything that you can talk about that addresses serology and comparisons that actually touch on the candidate vaccines that you -- that are being suggested to us so where we'd have some kind of an idea of, you know, what

to expect or how much better it is from the other, or anything like that in terms of this?

DR. WENTWORTH: Right. Yeah.

DR. BENNINK: I know it's difficult because they're usually at the last minute, but --

DR. WENTWORTH: The short answer to that is really I don't have data other than to say when we, you know -- it's hard to do the other analysis where you immunize something with it and show that it works better.

All I have is data saying these are the more reduced groups, which is the 5B and the 5A with the additional 187 and 189 substitutions. And that's the major piece of data that says -- and the fact that, you know, these are the viruses that predominate the circulation globally, you know. In the race with influenza to keep a little closer to that group of virus is a good idea.

DR. BENNINK: Does the FDA have anything from that as well with using the candidates? Any sera or

anything else?

DR. WEIR: Actually, I don't think we do at this point. I mean, we saw the information just last week, too.

DR. EL SAHLY: Okay. Dr. Meissner?

DR. MEISSNER: Yeah. I have a question I think both Lisa and you can answer. The overall vaccine effectiveness or the preliminary VE was pretty good at 45 percent, and it was pretty narrow confidence intervals. But looking at individual age groups such as those over 50 years of age, the confidence intervals got to be pretty wide.

Is it possible to break down who got adjuvanted vaccine or who got high-dose vaccine, or are the numbers simply too small to -- could that be an explanation, in short, as to why the confidence intervals are very -- are as wide as they are? And then secondly, could you just remind me -- I think I understand why you have both cell-based and egg-based strains. And it's presumably, I guess, because one

grows better in eggs. But could you just say a few words about that and why you selected that?

DR. WENTWORTH: I'm going to make a suggestion to have Lisa start with the first part of your question, and I'll take the second part of your question.

CAPT. GROHSKOPF: That sounds good. So for the issue with numbers, numbers always end up being an issue within, I imagine, with any surveillance network for VE, but, you know, I can speak particularly for ours. As far as the specific question of adjuvanted vaccine and, you know, knowing who got what kind of vaccine, whether it was adjuvanted or other vaccine types, we don't have any of that information yet. At this point, this is a preliminary result, and, you know, as time goes on, they will be going into confirming what type of vaccine was received.

In the past, in general, it's been difficult giving the numbers to get vaccine-specific estimates. For the most part, probably the greatest success for

the greatest number of years was with LAIV versus inactivated vaccines among children. But, for example, there haven't even been that many years that have been sufficient use, for example, of high-dose to provide a separate high-dose estimate. The VE network sites are not told which vaccines to procure and use, so it's not something that is prescribed. So there's -- we basically find out at the end what got used and determine whether there are enough numbers.

There are smaller numbers obviously for, you know -- the more we stratify whether it's by age or type or subtype. When we get to H1 -- and this is, you know, alluding to the question earlier, you know -- we have relatively small numbers of H1 which is -- relatively small numbers for the older age category which is why we had a collapse. And that's unfortunate, I think, just the nature of the beast as far as the surveillance and the VE network work goes. They were able to break down for H1N1 the adults into two different age groups, but, as you saw, 18 through

49 is still a relatively small category.

In the recently published estimates from Canada where they had bigger numbers, they do have a somewhat tighter estimate. I think, you know, all we can do now is just see and watch as time goes on to see as we get more numbers whether we can get more precision in the estimate that we have.

DR. WENTWORTH: Okay. And so the second part of your question related to cell vaccine strains versus egg vaccine strains and why we have differences, this is the first year where we've actually listed the cell vaccine strains right at the header, and that's in part to avoid confusion. They've actually been being selected since cell vaccines were available. They've just been in the reagent and CVV tables on the WHO website, and so manufacturers of the various types of products or manufacturers interested in making something new could go and find the right virus to use.

In part, we used to get a lot of questions about which is the proper cell one to use, and so

that's part of the reason they're now just officially named, right along with the egg viruses. And that may help academics as well discern some of these differences. If you remember, only two of the WHO CCs have the qualified manufacturing cell line available to isolate cell CVVs from, and so what has to be done is we have to name a cell prototype virus that can be isolated in regular cells, either MDCKs for H1s or MDCK SIATs for H3s, that any of the CCs can isolate and grow in their own laboratories.

And so sometimes we disseminate one of those regular cell culture viruses to all the CCs, if at all possible. A good example is this case, the Hong Kong/45. That was one of our serology engines used. It was selected a long time ago when we saw that group emerging. So we used it as a serology engine. We also had disseminated it to all the other CCs so they could make different ferret antisera against it and test their viruses with it.

And so that allows us to have this kind of

cell candidate and, say, for example, its counterpart Guangdong-Maonan/SLW/1530 -- I've probably forgotten the number. But that one, if you look at the original clinical specimen of the Hong Kong/45 and that virus in the HA, they're the same. And so it's kind of the name is different.

Now, as you illustrated, once you get an egg isolate, you get additional substitutions. That virus has substitutions at 225 and 186, which allow it to replicate efficiently in eggs. And the cell culture isolate for that virus actually had a mixture in it. So the cell culture isolate for that particular egg virus that had pretty good antigenic properties couldn't be named because it wouldn't be a clean antisera.

So in part they're named because only two CCs can grow the cell CVVs, and they have to be passed in a two-way antigenic test against a named prototype such as Hong Kong/45 or Hawaii/70 in the H1N1s. I know it's kind of confusing because we're breaking new ground

here, but that's how the system's working.

DR. EL SAHLY: I want to take this time just to see if anyone else besides Lisa is on the phone and if they have questions. Okay. Well, we earned a break, a 10-minute break, and we will reconvene at 10:50. Thank you.

[BREAK]

DOD VACCINE EFFECTIVENESS REPORT

DR. EL SAHLY: Dr. Mark -- I'm sorry, Mark Scheckelhoff from the Armed Services Health Surveillance branch is going to review the Department of Defense vaccine effectiveness report. Dr. Scheckelhoff.

CDR SCHECKELHOFF: (Audio issues.) Is that better? Am I on? Okay. So again, good morning. Thank you for the opportunity to share the DOD influenza surveillance data. As I mentioned, my name is Mark Scheckelhoff. I'm with the Armed Forces Health

Surveillance Branch, the Globally Emerging Infections Surveillance Program. Again, just as kind of was done by CDC, this is going to be broken up into two different sections. They'll be a brief discussion about the circulating strains that we observed in DOD, a discussion of the phylogeny of those viruses, and then we'll switch topics and cover the vaccine effectiveness.

So brief snapshot of the DOD surveillance network, about 400 locations in over 30 countries covering both U.S. military as well as foreign military and some foreign civilian. It includes partnerships with multiple ministries of healths and international universities as part of that network. All of our CONUS, so United States and overseas laboratories, do have extensive characterization capabilities, at least molecular detection, PCR, and sequencing capability as well.

We share that data with CDC and WHO reference centers, and that typically ends up being about 30,000

samples a year. We also have an epi analysis capability, as I think many of you are aware. We have a repository of all the DOD clinical data. And the epi analysis group within Armed Forces Health Surveillance is able to pull that data and query it to generate these types of results.

This is just a quick snapshot of the map where the different countries that contributed to the report and the data that I'm going to be sharing with you today. The stars are the kind of key laboratory locations of DOD laboratories across the globe. So I wanted to present this a little bit differently than how I have in the past. This is a quick snapshot of the circulating viruses that were detected and that are going to be shared. I just want to share this briefly to kind of provide a snapshot with the surveillance network with the DOD. You notice that the blue are H1N1, the red are H3N2, the green are influenza A not subtyped, the purple are influenza B Victorias, and the light blue are actually AB coinfections so. And

there's basically no Yamagatas detected.

I provide this first, as kind of an introduction to say that, you know, we wanted to just provide a quick snapshot to show that the DOD data that we're observing is very similar to what the WHO has presented for these particular countries. But also, with the surveillance network, we don't have nearly as many A un-subtyped. All of our locations are able to provide subtyping so it provides a little bit different level of resolution to that data.

So starting off with North America. As you can see, the epi or the incidents of circulation is very similar. Again, this is primarily United States, although it does include some border populations. As with the other presentations of data that you've seen so far today, on the left axis is the number of specimens. The epi week is the horizontal axis and then on the right side, the percent positive. So again, not really much difference. The influenza B was predominating early in the season, and that's been

replaced predominantly with influenza A H1N1.

In South America, there was a slight difference in the data that the DOD generated as opposed to WHO. This is primarily from Peru, Paraguay, Columbia, and Honduras. We see a slightly higher proportion of influenza B in our populations. H1 and H3 have kind of co-circulated in equivalent amounts, but I think, with the WHO data, they've been observing on those countries a little bit higher proportion of H1N1 than we were seeing in ours.

For the European region, again, slightly different. We see a slightly higher proportion of H1N1 in the countries that we're doing surveillance in, which include Belgium, Germany, Italy, Spain, Turkey, and the UK. Again, some of the WHO data is A un-subtype, so, you know, that might be H1N1 that's circulating and just not identified. We have seen relatively consistent rates of influenza B also circulating in that region, but I think that's consistent with what other groups have seen.

In the Middle East, again, similar, we have a little bit higher proportion of H1N1, but I think that's because the other data is showing a lot of A un-subtype, again, consistent circulation of influenza B. And I should note, I think it's obvious at this point that, when we're talking about B, we're obviously talking about B Victoria lineage for all these different groups. For East Africa, again, this one we saw a little bit different pattern. We had a much higher spike of influenza B early in the season. That has kind of dwindled off, similar to what the WHO data has seen.

And then so for East Africa this includes primarily Kenya, Uganda, and Tanzania. And then West Africa, the primary country we're looking at is Ghana. This is basically identical to what WHO has shown. I think basically our lab there is one of the kind of primary contributors to that data, so.

And then finally looking at Asia, again, fairly consistent with what the WHO has generated.

We've seen a little bit more proportion of H3N2 but again, predominantly looking at the circulation of A H1N1 in our Southeast Asia populations. And for this data, we're primarily looking at Thailand, Cambodia, Laos, Nepal, Bhutan, Philippines, as well as South Korea and Japan.

Okay. So just quickly to summarize the circulating subtypes that have been observed in the DOD network, again, North America, predominantly United States, there was the early predominance of influenza B that was replaced later in the season by A H1N1. In South America, we showed the predominance of influenza B. While in Europe, again, H1N1 is predominating. Asia, we did see some early predominance with A H3N2 with a more recent predominance of H1N1. In the Middle East, it's been predominantly H1N1. And then with East Africa, kind of a mixed predominance of B with a kind of recent uptick in H3N2 as well as H1N1, and then in West Africa it's been predominantly H3N2 in that region.

So I wanted to now move into the phylogenic analysis. This has been performed and consolidated by the United States Air Force School of Aerospace Medicine, USAFSAM, the folks out at Wright-Patterson in Dayton, Ohio. So this is just quick snapshot that shows the total number of isolates that have been sequenced, where they came from, and the subtypes. So not surprisingly because, you know, we needed a little bit of lead time to be able to have that data for this discussion, the available strains for North America were predominantly in the influenza B Victoria strains with, you know -- we tried to get as many of the new H1N1s that were emerging as we could. There's just been low circulation of H3N2, so we don't, at least on the North American side -- don't have a lot from there.

Unfortunately, we were only able to get H1N1 strains out of Africa. We weren't able to get any of the H3N2 strains out of the West African, the Ghana countries, where that's been predominating. But then again in Europe and Asia, we got a little bit higher

proportions of H3N2 but, again, a fair proportion of H1N1s as well.

So I want to start off with the influenza A H1N1 hemagglutinin phylogenic tree. So again, just a little under 770 specimens that were sequenced, all clade 6B.1A with that 183P substitution, similar to the other data that's been demonstrated or displayed thus far. Almost three-quarters of the subtype or subgroups that we're identifying within the H1N1 6B.1A clade belonged to the subgroup 5A. About 15 percent are from the subgroup 5B, and a much smaller amount are within the subgroup 7. So -- oh, yeah it's working.

So this is the 5A group here, this large group here. The 5B are here, and the 7 are here. Also kind of similar with the global trends, about 90 percent of our 5A viruses have this D187A and Q189E substitution. We've also been tracking a fair number with this K130N. We don't have a lot of the N156K substitutions.

But some interesting things that I wanted to highlight in this tree, so similar to the way Dr.

Wentworth presents it, you know, down here we're looking at the month that these isolates were obtained. The color-coding, orange for the African region, kind of a pinkish color for the Middle East, green for Europe, red for India and the Asian countries, and then blue for North America, and then the black is a reference. But we've also broken it up here based on vaccination status. So each one of these triangles is representative of the virus -- of the specific virus that was sequenced and whether that patient or where that specimen came from was either vaccinated in a blue triangle or not vaccinated in this kind of pinkish color, salmon-colored triangle. And then also if you notice, there's little red Hs across the line of the tree. Those were ones that we were able to identify as being hospitalized or having severe disease.

So when you look across the tree, you see that the vaccination status of these patients is fairly well distributed in terms of there doesn't appear to be one specific subgroup which is emerging or is breaking

through vaccination, at least nothing that you would be able to consider any kind of -- with any kind of statistical significance. I think interestingly, you know, we were -- Dr. Wentworth was discussing this N156K and showing there were some anagenic differences.

There does seem to be a bit of a clustering of vaccinated individuals here that are still, you know, coming down with influenza. There is also kind of interestingly this, at the very top of the tree, another one of these little clusterings where it looks like there's a fairly concentrated group of vaccinated individuals that are, again, kind of seeing a breakthrough with infection. So interestingly, those are coming from primarily our Southeast Asia countries. This group seems predominantly to be from the North American isolates.

So then just kind of summarizing the emergence of the clades, I think this is consistent with what's been seen on a global basis that the 6B.1a5A has kind of -- sorry -- has been kind of slowly emerging as the

predominant H1N1 HA subgroup. 5B has -- we've kind of continued to see it expand as well. And we haven't really seen too much expansion out of the subclade 7.

Now moving on to the H3N2. So again, we only had about 150 of these specimens from this season. Again, similar to kind of the trends that have been observed elsewhere, almost all of those are 3C.2a1b. We saw very few 3C.3a viruses. Again, looking at the kind of color coding, predominantly the ones that we got were from Europe, United States, and then one from Southeast Asia.

In looking at the kind of the much larger group, the 3C.2a1b viruses we're tracking, about 70, 75 percent of those have this T131K substitution that was, you know, again discussed by Dr. Wentworth. We see a slightly smaller proportion that have the T135K, and we really haven’t seen, at least to this point, many of those viruses that also have the additional S137F and those other substitutions that Dr. Wentworth was discussion. And I think we were -- yeah. So we see a

very, again, very kind of small portion of those that we've sequenced thus far that have those additional substitutions. So the predominantly, what we're observing in our populations is the bulk of them have the T131K.

And then also similarly, you know, just kind of looking back over the past couple seasons and the trends within the H3N2, you know, we kind of discussed this in a bit in the questions from the last talk with Dr. Wentworth. You know, we've seen this kind of trend of the 3C.1a1b's that have always been kind of lingering and hanging around. We saw that emergence of the 3C.3a viruses late last season or a little bit later in the 18 -- '17-'18 season but then the huge expansion of that in last season. And then during this season, we've seen almost no circulation of those amongst our populations. We've really -- even though the numbers are relatively low, it's been predominantly the 3C.2a1b.

In looking at the influenza B Victoria, again,

we've had about a thousand isolates for sequencing, again, due to that early spike in influenza B Victoria cases. Almost a little over 95 percent of the isolates that we've sequenced are the B1A3, the 3-deletion strain. Only, you know, a very small proportion is still the B1.1a1, the two-deletion strain.

Again, looking at the, you know, those that are vaccinated versus unvaccinated and those that are hospitalized, we saw 19 collected from hospitalized patients. You know, basically all of those were from the three-deletion strain. Almost all of ours has the G133R and K136E substitutions, and about half of them also have this additional E128K substitution. We did have ten Yamagata specimens that were collected, and they were all the same clade. Again, we didn't bother putting the data on because that tree is fairly nondescript at this point.

Okay. So again, just reviewing the circulation and kind of the emergence of these clades, you know, as we discussed last year, you know, we were

seeing some of the three deletions in our Southeast Asian populations. It was still -- at the time of this meeting, was still kind of consistent with or proportional to the number of the B1A1 strains. And then obviously the circulation changed dramatically, and we see much higher incidents in the current season.

So this is surface protein similarity. This is basically the average protein similarity based on the month, so cumulative for all the isolates that were sequenced in the given month and then color-coded based on the different viruses. So again, Yamagata's typically the highest because there hasn't been much divergence. Kind of not surprisingly, the H3N2 tends to be the lowest because of the vaccine strain being the 3C.3a, and the predominantly circulating strains are the 3C.2a1b's. But then you do see, I think, predominantly because there has been a couple 3C.3a isolates that have popped up lately, you actually see some increase in the overall similarity of those viruses later in the season.

So this is -- I don't want a spend a lot of time on this. This is just a -- it's -- on the left you have the H1N1 viruses, on the right the B/Victorias. On the left side of the panel is the hemagglutinin. On the right side, the neuraminidase and the same for the Victoria.

Basically, this is just looking for major reassortant types of activities. The fact that there are some kind of crossing bands but they're all within the same clade suggests that there's no major reassortments going on. Again, this is kind of a rough sketch, but what it -- the takeaway message, in brief, is just that, amongst the viruses, that we're sequencing, there doesn't seem to be a major reassortment.

Okay. I just want to go through these very briefly. Some -- we've stood up a capability to do microneutralizations so we could start to look at some of the reactivity of the viruses that we're isolating across our network, first for H1N1, so looking again at

reference strains from the current vaccine and some of the previous historical strains to viruses that were isolated over the course of this past year. These first, I think, four are 5B clade. And then you have the next about six that are the 5A clade, or subclade. And then these last two here are from the subclade 7.

I think what you can basically kind of see, we're still working through some technical issues with the assay that have kind of caused some overly inflated numbers here, but we are seeing some decent similarity and reactivity of the current strains despite, you know, the emergence and kind of divergence that we're seeing on the phylogeny. We are still observing a fair amount of reactivity and, as you would expect, you know, more similar to the Brisbane strain than, you know, the previous Michigan and California strains that are, you know, a little bit more antigenically distinct. Then similarly for the H3N2, again, we didn't have a lot of numbers to work with for this analysis.

Essentially, these first five are -- these are all 3C.2a1b. The first five or so are the T131K substitution viruses, and then we have, I think, these two are actually the T135K. But again, you know, kind of surprisingly, we're still seeing a fair degree of similarity or, you know, reactivity with the circulating viruses to the vaccine strain and to the historical strains despite the fact that it is antigenically very, very different.

And then the B/Victoria, again, I think this has been kind of a surprising result that other people have indicated that, despite the fact that the two-del and the three-del, you know, are pretty different. You know, all of these are 3-deletion strains, but we're still seeing at least some level of reactivity amongst the viruses that are in circulation. When you look at just a kind of brief snapshot in terms of how you're defining it, again, caveat this with this is still some preliminary data, but primarily the H1N1s that we're looking at still seem to be fairly reactive to the

vaccine strain. H3N2, most of them are and same with Victoria. We did have one Yamagata in there, I forgot to mention, and that, of course, was very similar to the vaccine strain because there hasn't been really any divergence.

Okay. So transitioning to the vaccine estimates, so these are mid-year estimates provided in part by, again, the folks at USAFSAM and NHRC, Naval Health Research Center, as well as the Epidemiology and Analysis Section at AFHSB. These are all case test negative control studies, all studies, again, using verified positives. There is a slight difference in terms of whether rapid positives or strictly RT-PCR was used for the method, but I'll cover that with each section. Oh, yeah, it's right there.

So essentially the USAFSAM analysis included only PCR viral culture. The AFHSB, which is the service member VE estimate, also used positive rapid tests but excluded rapid test negative. Then that analysis, we performed it for all influenza types and

subtypes that, you know, essentially our data would allow for.

So starting off with USAFSAM analysis. So this population includes DOD beneficiaries as well as some civilian populations along the U.S-Mexico border that sought care in some of those remote clinics. These are adjusted estimates for effectiveness. Again, this does not include service members.

We were able to do the analysis overall influenza and then by B, all told B. We didn't have enough Yamagata, obviously -- by A across any subtype, and then specifically for a H1 and then a H3N2. One caveat, again, relatively low numbers of H3N2, so we didn't have enough data for the higher age group for that. And then the data was adjusted for age, time of specimen collection, location, and gender.

This is just a quick snapshot of the populations itself and the cases of influenza that were observed as part of the study. So again, these are laboratory positives, people that have sought care at a

local MTF. Again, predominantly amongst the cases and controls, influenza B was the predominating strain, A H1N1 coming up right behind it.

We had a little over 1,500 cases, again, confirmed by RTPCR and culture. Controls, a little over 2,100 test negative. Vaccination rates of cases was about 43 percent. Vaccinate rate of control was about 57 percent. Again, proportions among the cases, specifically of total influenza, are similar to what you would expect based on the total number of influenza cases in the entire population.

Again, just to further breakdown of the populations, so I just want to jump right into the actual results. So in looking at our VE estimates among, again, beneficiaries and some additional civilian populations, overall, so not discriminating between influenza A or influenza B, we see rates of about, you know, 54 for all age groups for children. So under the age of 18, it's about 47 and then for adults around 48 percent.

When looking specifically at B, again, B overall -- it hovers around 50 percent and then within the child and the adult populations, again, right around the 50 percent range. A for A-all subtypes, again, not discriminating based on age group, just overall, it's about 45 percent. The children -- the rate of VE in children is a little bit lower at about 38, and we're actually seeing a little bit higher rate in the adults at 55 percent, which is, you know, pretty different than what we were just discussing with the CDC data.

One thing I will just quickly mention, if you look at the -- our total number of cases in those, we do have a fairly larger number of cases that we're pulling from for this analysis. So it may be that that's part of the reason why we're, again, starting to see a little bit higher rate than what's being reported by some other groups. And then --

DR. EL SAHLY: Dr. Scheckelhoff, if I may interject, I see you are almost halfway through the

talk, but we are already way over time.

CDR SCHECKELHOFF: Oh.

DR. EL SAHLY: I wonder if you have summary slides--

CDR SCHECKELHOFF: Sure.

DR. EL SAHLY: -- that you can share instead? Sorry for this.

CDR SCHECKELHOFF: Yeah. So we can go on to -- again, service member, this is something that we've discussed before. Essentially, because this is such a highly vaccinated population, when you look at the vaccine effectiveness for these different groups, you see very low levels of VE for, especially, the influenza A subtypes. Because the influenza HAH3N2 has been kind of sporadic throughout the season, we're actually getting better estimates on the VE for those specific populations.

I will note that the analysis for the service members for A overall and A H1N1 was limited to the last two months basically because there was no H1N1

circulation early in the season. So it wasn't deemed to be a fair comparison to identify those or include that those first couple months of the season when there was no circulation of H1N1 and there was basically no opportunity. And when those dates -- when that additional data was added in, it further skewed the numbers. So we are seeing a significant level of protection for the H3N2s, again, not for A and not for the influenza B except for well -- I'm sorry. In the adjusted B, we do see a low to moderate level of protection.

So this is, again, just the overall snapshot of the VE dependence. We see, you know, moderate protection in most of the populations, except when you're talking specifically about service members, which again, highly vaccinated population. So with the A overall and the A H1N2, you don't see significant levels of population service members. You do see it in the AH3N2 as well as kind of low to moderate protection in influenza B. And that just summarizes that.

So then just, you know, basically to wrap up, we had to submit these prior to the WHO coming out with their recommendation, but our recommendation was essentially the same. Identifying a 6B.1a subgroup 5A representative virus with those two amino acid substitutions which was the selection. Consider converting back to the 3C.2a1b clade virus, which, again, was the selection by WHO converting to a three-del representative virus, which the Washington strain also accomplishes that. And then sticking with the current B/Phuket strain.

Okay. So thank you. Just -- this is the work of a very large consortium of people, so I just want to take moment to thank them, especially the folks at NHRC, USAFSAM, and all the folks at Armed Forces Health Surveillance Branch.

QUESTIONS AND ANSWERS

DR. EL SAHLY: Anyone has -- we probably have

room for one question. Dr. Offit.

DR. OFFIT: When we first had trivalent vaccines, we would have always an H1N1, H3N2, and B vaccine representative. And when we had a quadrivalent vaccine, we added a second B. But in theory, there's no reason that we have to do it that way, right? I mean, if we thought for example that there were two claves of H1N1 or two claves of H3N2 or two claves of B that we thought were important and that we would think one say, Yamagata strain, was not going to be an important player next year.

We don't have to lock into that paradigm, right? So -- but it seems to me we always do it that way. I mean, just -- I guess this question is for you and Dave and Hana. Don't we have the option to do something different?

CDR SCHECKELHOFF: Yeah, we do. I think the primary question -- and I think we discussed this last season here -- was the level of regulation and approval that it would have to go through because that would be

considered a major -- so I guess I would defer to the FDA in terms of the process that would be needed because I thought there was some additional steps that would be required if we made a dramatic shift, not just in the subclade of the virus but actually the -- more of the composition of the virus itself. Is that not accurate? Am I misremembering the conversation from last year?

DR. EL SAHLY: We did bring up multiclade vaccines for H3N2, but I don't know that we got anywhere.

CDR SCHECKELHOFF: Yeah. To answer the question, yes, it's certainly something to consider. I think maybe part of the conversation that we had last year was because the WHO had postponed the selection of the H3N2 component. We were already kind of behind in terms of the manufacturing processes and making sure that it was available to then have to kind of reconvene and decide what that fourth component of the vaccine would be, depending on which way the WHO went with

their H3N2.

But in my mind, you know, circulation of Yamagata has been very low in most of the populations we're looking at so does it make more sense? I think Dr. Wentworth made a good point that, you know, I think we're seeing some relatively good levels of protection with the H3N2, primarily because of memory. So now that we've exposed people to the 3C.3a vaccine this year and they had some exposure last year then, you know, maybe some of that memory will also kind of carry over for those strains.

DR. OFFIT: But you could, you or Dave could say, look, we think that there are possible two circulating clades for H1N1, H3N2 that should be considered for inclusion in the vaccine, right? I mean, you could in theory say that.

DR. WENTWORTH: Well, I think I'm going to turn it over to Dr. Weir, but basically there is a formulation change if you are including two H3s.

DR. WEIR: Yeah, I think you're right. I was

having a little trouble following what you were getting at.

DR. WENTWORTH: Oh, sorry.

DR. WEIR: But no, changing something like that would require a complete change to the manufacturer's license. They would have to have clinical data to support it, for example. So no, what they are licensed for now for a quadrivalent is an influenza AH1 plus an influenza AH3 plus the two Bs. Mixing that in some other way, again, they would have to have clinical data to change their license, just like they had to have clinical data to add the second B strain to their trivalent license.

DR. WENTWORTH: But if it were done, it would be possible to made recommendations for such a thing.

DR. EL SAHLY: All right. Thank you everyone.

CDR SCHECKELHOFF: Thank you.

DR. EL SAHLY: Thank you, Dr. Scheckelhoff. Dr. Manju Joshi, the lead biologist at the Division of Biological Standards and Quality at the Office of

Compliance and Biological Equality, CBER, FDA will go over the candidate vaccine strains and potency agents.

CANDIDATE VACCINE STRAINS & POTENCY REAGENTS

DR. JOSHI: Getting close to the lunchtime and we are, I'm sure, running short on time so I will try to keep it short. Excuse me, is this pointer not working? Okay. That's okay.

So I'll give you a quick update about the candidate vaccine strains and potency reagents for 2020-21 northern hemisphere influenza season. You have been hearing all the strain names from the first thing in the morning, so I'll try to keep them as short as possible, so we save time. So during my talk, I'm going to cover four different things. I'll give you a list of currently used northern hemisphere vaccine viruses and what are WHO recommendations for the upcoming northern hemisphere campaign for both trivalent and quadrivalent vaccine.

I'll give you an idea about what is the status of available potency reagents for each of the viruses that are recommended. How do -- and lastly two points, I would like to -- that are not so much to the committee but for the other audience, the manufacturers in the group here, for how we are planning for the '20-'21 campaign and some general comments which help us in running the operation very smooth.

So coming to the H1N1 strain influenza A strain, the current vaccine virus was the A/Brisbane/02/2018, pdm09-like viruses. And as all of us know, that for egg-derived vaccine IVR-190 reassortant for A/Brisbane/02/2018 was used, for cell-derived vaccine and A/Idaho/07 was used. And a virus sequences from A/Brisbane/02/2018 was used for the recombinant HA vaccine.

So last week, WHO recommended the new strains and the recommendation is for egg-derived vaccine for the upcoming northern hemisphere season be A/Guangdong-Maonan SWL1536 like virus. A candidate vaccine virus

which is the reassortant CNIC-1909 is available. For cell culture and recombinant vaccine, WHO recommends A/Hawaii/70/2019-like virus. And currently a two-candidate vaccine virus, the cell culture derived one available is the A/Nebraska/14/2019.

If the committee approves of inclusion of these WHO recommended strains in the vaccine, reagents will be needed for the future testing, and CBER will work with essential regulatory laboratories and manufacturers to prepare and calibrate the required reference antigens. And we are already planning for the sheep sera production.

Coming to the H3N2 influenza A strain, for the 2019-20 season, A/Kansas/14/2017-like virus were recommended. For egg derived vaccine, reassortant X-327 for A/Kansas/14 was used. For cell-derived vaccine, A/Indiana/08/2018 virus was used, and, similarly, for a recombinant vaccine A/Kansas sequences were used.

WHO recommends that virus for 2020-21 northern

hemisphere campaign include A/Hong Kong/2671/2019 virus for egg-derived vaccine. And currently, a reassortant NIB-121 is available for this virus. The recommendation for cell and recombinant vaccine includes a different A/Hong Kong, which is A/Hong Kong/45/2019-like virus, and currently a candidate vaccine virus available out of A/Delaware and A/Minnesota/41. Again, I will emphasize if today committee decides that this be the part of the vaccine, we will work your ERLs and manufacturers to prepare and calibrate the required reference antigens. And we are already thinking, because it's a very quick turnaround on everything and we are to be upfront -- so we are already planning about the sheep sera.

Coming to the influenza B from B/Victoria lineage, for 2019-20 season, B/Colorado/06/2019-like virus was recommended and B/Maryland/15 wild type and it's reassortant BX-69 were used by vaccine manufacturers for egg-derived vaccines. For cell vaccines, a B/Iowa/06/2017 were used, and, for the

recombinant vaccine B/Maryland/15 sequences were used.

During the 2020 southern hemisphere season, there was a change recommended, and for southern hemisphere campaign, WHO had recommended the B/Washington/02/2000-like virus. And come for the upcoming '20-'21 northern hemisphere campaign also, the recommendation says that the B/Washington, B/Victoria lineage virus for a trivalent vaccine. So since it was recommended for southern hemisphere, it is in a better shape. We have things ready. Currently, a wild type virus for B/Washington, as well as for B/Victoria/705/2018 virus and its reassortant BVR-11, are available. And there are several other additional candidate vaccine viruses are available for this strain which can be exist -- a list can be checked at the WHO website I have cited here.

For cell culture-derived vaccine, the recommended virus sublevel is B/Darwin/07/2019 and similarly for a recombinant vaccine in B/Washington/02 wild type sequence can be used. So since it was

recommended for southern hemisphere, all of our ERLs have worked towards making the reagents. And here is the current status of the potency reagents that are available from CBER and other ERLs.

CBER and both in CBER and NIBSC have prepared reference antigen for B/Washington wild type viruses, and they are available. CBER has the reference antigen lot and the first antiserum lot 1914. And we have additional lot with preparation already planned for it.

For B/Victoria BVR-11 reassortant, both to ERLs DG and NIBSC have prepared reference antigens, and antisera and they are available from them. Similarly for the cell-derived B agents for B/Darwin/07/2019, NIBSC had prepared reagents during the southern hemisphere campaign. And CBER has also prepared these reagents, and they are under calibration right now. And at the same time, we are working currently to have the reference antigen reagent calibrated for B/Washington recombinant HA vaccine platform.

Coming to the influenza B from the B Yamagata

lineage, all of us have been with B/Phuket forever. I'm sure a lot of people wanted it to go away sometime, but it just stays with us forever. And since it has been around, things are in a better shape. The various candidate vaccine viruses which are being used were the B/Phuket wild type and its reassortant, BVR01B. For last year for cell culture vaccine, B/Singapore/INFTT-16-0610/2016 was used, and similarly B/Phuket sequences were used for the recombinant vaccine.

WHO recommends that for the quadrivalent vaccine the second B strain, B from the B/Phuket-like strain from Yamagata lineage. So if you go to the WHO website, there are a whole list of all the level candidate vaccine viruses. Coming to the availability of reagents for vaccine testing, these reagents have a lot available from CBER and other ERLs. Wild type B/Phuket have been available from CBER since it was first introduced in the vaccine. Both reference antigen and several lots of antiserum are available.

Just for the sake of convenience, I have

pointed out that we have all lots with asterisks up there because those lots are really getting depleted, but we do have a new lot already ready. Both NIBC, TGN, NIID also have the reagents for wild type B/Phuket. For BVR-1B, TGN had prepared last year a reagent, and we had helped them with the calibration of the reagent. For B/Singapore/INFTT, the cell-derived candidate CBER had prepared the reagent, and those are available.

There was another virus which was not -- was used at some point, which is B/Utah-like, which is also a B/Phuket like virus. And we do have reagent for that as well. And currently, CBER is in process of calibrating a reagent for B/Phuket for the recombinant HA platform.

So just the last two slides, quick one is not so much for the committee but it is for the manufacturers who are in the audience. We want to make sure that our flu campaign runs smooth. I know all of us work under a very tight timelines to achieve one

single goal that we can have vaccine being delivered in the right timeframe to the public. So I would like to request to all the manufacturers, whoever is in the audience is, that they should be able to provide us the information regarding the strains they plan to use -- well, once they are selected by the committee today -- which reassortant they are trying to focus on, what are their plans about reference antigen, which reference antigen and lot numbers to use.

And I want to emphasize that it is very important for us to have this information so that we can plan our campaign and out activities here at the DBSQ CR duration, as far as reagent calibration process is concerned. If you are using some reagents from other years, we have to make sure that we import those reagents so there are no delays in vaccine testing. As all of you know, we do your drug substance, the monovalent testing as well, so it's very important for us to plan that. And subsequently, all the lots need to be tested, which comes in the second phase. So we

want to be prepared for it, and we would like to have this information so we can organize the whole program well and everything runs smooth.

And just lastly, like every year, I would like to make a few comment. As manufacturers, please remember that only CBER authorized reagents should be used in the test potency of vaccine marketed in U.S., so please consult with us when you are picking up reagents. And when you send our monovalent sample, please submit it to my attention, email me and those I have listed on the list so that we know how the whole process is running.

If you have any inquiries regarding CBER recommended standards and reagents, please contact CBER standards. I have provided you the website. And importantly, send us any feedback comments on the suitability or use of reagents or any questions you have because we have influenza feedback site in the mailbox up here, and we would be happy to help you out with that. So thank you.

DR. EL SAHLY: Thank you, Dr. Joshi. Any questions for Dr. Joshi? All right. Thank you.

DR. JOSHI: Thank you.

DR. EL SAHLY: Comments from manufacturer representative will be given by Dr. Penny Post. Dr. Penny Post is head of Regulatory Affairs at Sanofi Pasteur.

COMMENTS FROM MANUFACTURER REPRESENTATIVES

DR. POST: Thank you. Good morning. I'll also try to be brief, since this is the last talk before lunch, and we're running a bit behind. So first, I'd like to thank VRBPAC and the FDA for the opportunity to share the industry perspective on influenza virus vaccine manufacturing. I'm making this presentation on behalf of all manufacturers who supply influenza vaccine to the U.S. market. These are AstraZenenca, Seqirus, GSK, Protein Sciences, and Sanaofi Pasteur. Each manufacturer has contributed to

this presentation.

So today, I'd like to give you an overview of our vaccine production, release, and distribution timelines, the preparations that we make with the public health service organizations throughout the year, and insight into the challenges that we face as vaccine manufacturers. Let's see if I got this -- okay. So as you heard at the beginning of the meeting, I'm required to disclose to you that I'm employed by Sanaofi, and I own stock in the company.

Okay. So we as vaccine manufacturers consider ourselves partners with the public health service to help protect against influenza, and we appreciate the challenges today in selecting the best strains for the vaccine to be used in the next influenza season. This requires the balancing of three objectives.

It is, of course, a top priority to have a vaccine that's well-matched to the circulating strains. The time needed to select the best strain needs to be balanced with the time needed to produce and to

distribute the vaccine before the start of the influenza season; however, we cannot predict exactly when the influenza season will begin. In some years, this may be as late as late October and, in others, late December. Lastly, we need the time to be able to produce enough influenza vaccine to immunize all those for whom vaccination is recommended. So basically, we want a well-matched vaccine before the start of the influenza season and enough vaccine to produce -- to protect all those who need it.

The amount of vaccine that has been distributed over time has been steadily increasing. The left graph here on the slide shows an impressive steady rise in total doses that have been distributed by the vaccine manufacturers over the past nearly 40 years. The right panel shows the pattern of vaccine distribution over the course of this past season, where distribution is largely completed by November. To date this season, over 174 million doses have been distributed, which is the highest annual amount for a

seasonal influenza vaccine.

Vaccine supply requires timely selection of well-matched strains, time to manufacture enough supply to meet this demand, and timely pre-seasoned distribution. Seasonal influenza vaccine supply is analogous to a relay race, where members of the team take turns performing their roles. The race starts with the viral strain work within the collaborating centers, the essential regulatory laboratories, and the high yield reassortant labs who then hand off to the manufacturers.

So key in a relay race -- key to winning is that the receiving running starts running before the handoff, so manufactures start producing vaccine at risk to be at full speed when the handoff to us occurs of the new strains and the new formation. There are special challenges for influenza in this relay, which include multiple batons in the race, such as multiple candidate vaccine viruses, multiple reagents, and multiple vaccine types, and multiple providers,

essential regulatory labs and high yield reassortant labs. In addition, we have hurdles in this race. We have manufacturing timelines.

The number of doses is rising year after year, and timelines are very compressed to be able to manufacture and distribute the vaccine. Moreover, today's manufacturers are largely supplying quadrivalent formulation and no longer trivalent or no longer just trivalent, which requires production of a fourth vaccine antigen. The Nagoya Protocol, which I'll discuss in more detail in a couple of slides, threatens timely availability of the best matched virus or DNA sequence.

Delayed changes is another hurdle, such as a delayed H3N2 strain selection in 2019, and unexpected changes, another hurdle, such as last year's unexpected H1N1 strain selection. Also of note, the market has moved towards specialized or customized vaccines over the past decade. And the more differentiated the vaccine the more sensitive it may be to delays, which

could create challenges in certain parts of the population who use those vaccines.

This slide gives you a snapshot view of the main activities each season that are done to achieve the U.S. supply timeline. In order to meet vaccine demand and to be ready for the baton handoff, manufactures begin to produce at least one of the three or four vaccine components at risk prior to the vaccine strain selection meetings using surveillance data that is available at the time. Once the annual strain selecting meeting occurs, as we've been talking about the WHO on February 28th this year and this meeting today for the U.S., production of all vaccine components begins and production of potency released reagents begins for any new strains, as we just heard from Manju's talk. If there's a strain change, new working virus vaccine seeds need to be produced.

Balancing manufacturing is done later in the summer to ensure that we have equal amounts of each vaccine component produced. Antigen yields from the

least productive vaccine strain are the rate limiting factor and determine the number of vaccine doses that are supplied and the supply timelines. We need potency reagents to accurately blend the vaccine components and, therefore, need to wait until these are available from the health authorities.

Vaccine is then packaged and distributed, and this process extends into the fall when vaccination is recommendation. So you can see it takes about six months to manufacture, release, and distribute the volume of vaccine doses required for the season. The number of doses is rising, and timelines are very compressed as reminded in the inset graph there on the bottom right corner. Additionally, as I mentioned earlier, today manufacturers are largely supply quadrivalent formulation which requires production of that fourth vaccine antigen.

So in summary, influenza vaccine manufacturer is determined by the need to distribute and administer vaccine well before the season peak, the availability

of the candidate vaccine viruses, strain materials, and critical potency reagents for the vaccine suppliers. And note, too, that the number of doses is rising over time. So if anything slips in this timeline, it will impact vaccine delivery for the annual vaccination campaign, which is the relay race analogy here.

Okay. For the next slide -- so as you can see with this tight timeline, for industry, unexpected changes add more risk. Last year's H3N2 strain selection was postponed by about four weeks by the WHO and about two-and-a-half weeks by VRBPAC. Human sera data are being used to ensure the best strain selection as we've been looking at today, but sera become available late in the process.

Industry starts to manufacture before the strain selection to ensure that the last doses can be delivered in time for the annual vaccination campaign, which largely ends in November. If the wrong strain is produced at risk, that material is lost and new product needs to be produced. Moreover, if the fourth strain

produced late in the season is of low yield, it can be difficult to manufacture enough of that monovalent bulk antigen to keep pace with the formulation activities. And finally, filling capacity for vaccine drug product is reserved in advance, with many of us producing in multiproduct facilities or contract manufacturing facilities.

There was a survey done of manufacturers on the impact of the late H3N2 strain selection that occurred last year. This was done for WHO. I know this is a busy slide, and I don't expect you to read it all. But I wanted to focus on some of the highlights here of the slide.

The impact of the delayed strain selection depended on the manufacturer and the vaccine type being produced. Feedback included -- there's some quotes from the slide. Completion of the campaign is extended by several weeks. First doses, while on time, will be of reduced volume, and the campaign will take two to four weeks longer. Mitigation of this risk was

possible by accepting additional costs and taking additional calculated risk and increased expenses by about 30 percent more.

So ultimately, last season vaccine distribution was timely but only due to factors that were outside the control of industry. So for instance, it was fortunate that the earliest available candidate vaccine virus was generally acceptable for use in manufacturing, although not for all manufacturers. It was also fortunate that calibrated potency reagents became available around the same time as in other years for the new antigen strain. So we didn't experience a delay there. And we were also fortunate that the source country of the candidate vaccine virus was not a signatory to the Nagoya Protocol and therefore did not delay strain availability or use of its genetic sequence.

Well, this slide we've been talking about today depicts the northern hemisphere strain recommendations over the past few years, with the

strains that have been changing over the years from the previous formulations shown in red. The last column shows the strain selected last week by WHO for the 2020-21 season. And for the first time, a cell and recombinant vaccine H1N1 strain was selected that differs from that recommended for the egg-based vaccine formulation.

So also to give you an idea of the work behind this, approximately 100 different viruses are evaluated annually by manufacturers, reassortant labs, and health authorities to be ready to provide the stocks for manufacturing. So we've been discussing the Nagoya Protocol over the past couple of years in our industry presentation, and I wanted to give you an update at today's meeting. As a little background, the Nagoya Protocol was developed from access and sharing discussions at the Convention on Biodiversity and has come into force in 2014 when the 50th region ratified the protocol. The objectives are to ensure access to genetic and related traditional knowledge for potential

use and ensure users and providers of genetic resources and related traditional knowledge agree on fair and equitable sharing of benefits arising from their use. These benefits may be monetary or nonmonetary.

This was initially developed for agricultural purposes, but it also covers viruses. Seasonal influenza virus strain sharing is in scope of the protocol, but pandemic influenza viruses are exempt. Under the Nagoya Protocol, national consent to access genetic resources is required and pre-agreed terms for fair, equitable benefit sharing prior to R&D work. Failure to comply may lead to accusation of biopiracy, litigation, product restrictions, a claim on income, or a halt in orders.

As of February 2020, 123 countries have ratified and entered the Nagoya Protocol into legal force. The time is about three months to formalize legal benefit sharing arrangements to use the influenza strain from each source participating country. The United States is not a signatory to Nagoya. Now, even

though the United States is not a signatory, countries could choose not to share with the United States companies, or there could be delays or restrictions on vaccine strain availability.

So I have a few recent examples shown in this slide. So of note, four candidate vaccine viruses recently had Nagoya Protocol authorization. Note that A/Switzerland/8060/2017 was a selected H3N2 strain for the 2018-2019 vaccine formulation. Four candidate vaccine viruses had tacit authorization, and three CVVs required material transfer agreements from the National Influenza Center to the WHO collaborating center and were not available in time and ultimately not used. None of these countries have asked for benefits, but, if so, then each manufacturer would have to negotiate the benefit sharing. And it could become too challenging to use the virus.

So as industry, we are concerned about the increase in the number of Nagoya Protocol impacted viruses, the increase in the time to provide

authorization, legislation emerging restricting the use of genetic resources that's independent of the Nagoya Protocol, and lastly, some countries are considering amending their legislation to include genetic sequence data and digital sequence information. So all of these risk supply delays are due to the required negotiation and/or notification costs by manufactures to address and resolve. So to summarize today, influenza is a serious disease with dangerous impact to chronic conditions, as well all know here. I share on this slide the CDC's disease burden pyramid, showing up to 45 million cases of illness a year, up to 810,000 hospitalizations, and up to 61,000 deaths annually in the U.S. since 2010. Impact on chronic conditions may go beyond even what's shown in this triangle.

So ensuring a robust vaccine supply for the nation is akin to running a relay race with multiple batons and multiple hurdles. There's a sustained increase in the number of doses supplied in the same time window. The Nagoya Protocol is impacting the

ability to select the best vaccine strain and strain sequence availability.

We also share that it's important to maintain confidence in influenza vaccines. We support the people follow vaccine recommendations, and we're willing to produce as many doses as are needed. We are all in this race together to ensure adequate vaccine supply and ultimately public health. Thank you.

QUESTIONS AND ANSWERS

DR. EL SAHLY: Thank you, Dr. Post. Quick question regarding the Nagoya Protocol, is the impact from the fact that certain countries are not signatories to this protocol, or is it from the fact that the U.S. is not? Which or both or --

DR. POST: No. I think the impact is that we may need to use a strain from a country that's a signatory. So even though the United States is not a signatory, we still have impact at the Nagoya Protocol

because we would have to, you know, address whatever may be needed from that country to obtain that strain. If we were a signatory, I think the impact would still be the same.

DR. EL SAHLY: Oh, so it would not matter who's signatory or who not?

DR. POST: Yeah, yeah.

DR. EL SAHLY: Okay. Yes, please.

DR. KURILLA: So the way the Nagoya Protocol is written, is it the sequence itself as opposed to the virus itself?

DR. POST: I think -- and I'm not a legal expert so there may be more -- there may be others in the room that could better speak to this, but I think it's -- today it's the virus availability. It's a little unclear about the genetic sequence. That may also be impacted, but we're not quite clear today on that.

DR. KURILLA: But if the sequence were published, you could theoretically make the virus on

your own, infect an animal, and then naturally isolate the virus --

DR. POST: I think that's --

DR. KURILLA: -- and that's still -- so is it just whoever says they had it first?

DR. POST: No, I think that's where it's a little unclear that what we would have to do to use that --

DR. KURILLA: So currently -- and I don't know if it's the case -- if China were, in fact, a signatory, they could not -- they could basically stop anyone else from making a coronavirus vaccine without a lot of negotiation is what they -- I mean --

DR. POST: Well, depending on what -- yeah, what they would require. That may be a potential. I'm not an expert on the protocol. I think the WHO has a lot of experience with it.

DR. EL SAHLY: Dr. Spearman.

DR. SPEARMAN: Thank you for that talk. That was actually really interesting. But one thing that

came out that I didn't realize was the point about industry starting manufacturing before strain selection.

DR. POST: Right.

DR. SPEARMAN: And how does that really work? Does everyone do that? Are you taking multiple potential candidate strains and getting them up to some level of production? How do you really do that?

DR. POST: I'll back up to that slide. Well, we use our own -- we use all of the available surveillance data that we can get to make our own decisions of what strain is least likely to change. And then, you know, we'll start making that. So that's why it's -- there is a big impact. You can see, if we've made the strain that we think won't change and then it changes, we have to throw that out and start over. But really because the timelines are so compressed, we have to get a head start.

DR. EL SAHLY: For example, this year all three changed, so I don't know if that's going to be a

problem.

DR. POST: Well, the three, four -- there was a fourth that didn't change.

DR. EL SAHLY: For the Phuket did not. Yeah, you're right.

DR. POST: Yeah, okay.

DR. EL SAHLY: Okay. Well, thank you, Dr. Post.

DR. POST: Thank you.

DR. EL SAHLY: Lunch break is next. We are scheduled to be here again at 12:50, please, 12:50.

MS. HAYES: For those who haven't already paid for your lunch, you can visit the kiosk right out front and pay for your lunch. Your menu selected items should be in your folders, if you've done that already.

[BREAK]

OPEN PUBLIC HEARING

DR. EL SAHLY: It's 12:51 and we will be now

doing the open public hearing session of our meeting. No one registered for the open public hearing session online or on the phone, but I want to invite the members of the audience in the room here if anyone wants to have a statement during the session. Raise your hand if you do have a comment to share.

Okay. I guess neither in person or online we have statements during the open public hearing, so we will now move to the issue of the discussion among the committee members of the strain selection for the northern hemisphere, 2020-2021.

COMMITTEE DISCUSSION, RECOMMENDATIONS, AND VOTE

DR. EL SAHLY: This is where I invite questions or comments, but I guess probably will ask many of them during the presentations. Dr. Bennink is thinking of a question.

DR. BENNINK: Yeah. I'll make a comment in a sense in this -- and I've talked a little bit with

David earlier that in a sense, I would like to see, you know, when we are sort of doing this, a little bit more data that actually you see where the candidate strains are actually used in the data and you can see comparisons or something like that with the serum and other things. And with the -- it was in the H3 and 2. There was some things there and stuff but, you know, in some of the other -- it's a little bit more if we could in the future, see more of that. It gives you a better idea of what the responses are and what the antibody titers are that we're seeing in terms of what the vaccines might generate or something along that line and how cross reactive they are about the strains that are circulating.

DR. EL SAHLY: Yes, it's certainly a wealth of data, and it would help to sort of zero in on some of the items or highlight them in a slightly different way. But yeah, definitely. Yes.

DR. WEIR: Can I just follow up that? Specifically, are you talking about you'd like to see

more of like the human serology data or what exactly?

DR. BENNINK: It doesn't -- all of it -- human serology is good, I mean, in that sense, but even in this particular case, in the H1N1, if you look at the tables, particularly the ones coming out of the WHO but also in some of the tables that David presented -- and maybe it's, you know, the labs haven't had it long enough, or they haven't had this. They haven't had time to generate antisera in the ferrets or in sheep or whatever so that -- you know, you're not really seeing or making comparisons of how much better it may be in terms of, you know, HI titers or other things along that line.

So I think what I saw was an absence of some of that data in terms of H1N1. Now, the H3N2, that wasn't as true and that wasn't the you know, the things. I just thought from that perspective we could have maybe seen something. I mean, we're being asked to select, you know, candidate strains which we don't see any data specifically for that strain in some

cases.

DR. WENTWORTH: Can I make a comment and ask a question at the same time? So guess there's plenty of data, right. And so I could spend the afternoon with you showing you data. So I think the question becomes should we remove some of the kind of surveillance like data that goes over where viruses are circulated and what's circulated and spend more time on, you know, HI tables, which I find that most people don't like? And so, even in the H1N1s, we had antigen and cartography there illustrating the vaccine strains that are named and their position. And then the H1s in particular, the ferrets don't differentiate these viruses that the whole reason we showed the human table was that humans do differentiate these viruses.

So in H1, it's particularly challenging. I'm happy to try to show more data, and I think Jack has a great point. And I'm happy to do it, but I think it would be at the expense of something because I, you know, I eliminated about 15 slides to get it down to

the 60 minutes. So I -- just tell us what you want.

DR. EL SAHLY: Dr. Spearman.

DR. SPEARMAN: So I have a suggestion. I think the data are great. It's great to see all the specific data. What I would like is a presentation, sort of a wrap up at the end.

Here is why we chose this strain. If you remember, here's the antigen and cartography, here's where -- you know, this is why we chose this subclade. And there was a debate about this maybe at WHO, but here's why we chose that strain. And then here's why we chose the next strain. So have that as the summary, very directed, why these are the best strains to go forward with.

DR. EL SAHLY: Dr. Chatterjee.

DR. CHATTERJEE: Just a follow-up to Paul's comment and that is that perhaps some of this information could be provided as background information to us before coming to the meeting so that we could review the materials ahead of time and more time could

be spend on discussion about why the strains were chosen.

DR. EL SAHLY: Dr. Kurilla.

DR. KURILLA: Yeah. I think one additional piece of data that would be useful is there's really no continuity over time with previous attempts to match the strain and the thinking that went into why we chose this strain. How successful were we at doing that, and when did it make a difference or when it didn't make a difference? We get this sort of interim vaccine efficacy currently, but how good were these predictions that we're making now?

How good were they two, three, four years ago when we were working with the very same equivalent set of data that sometimes we get it right, sometimes we get it wrong? But we don't get a sense of what are the critical parameters in terms of why we went with this clade over that clade when it worked and when it didn't work. That would be nice to see.

DR. EL SAHLY: Yes, Dr. Bennink.

DR. BENNINK: Yeah. Let me ask a different question that isn't so much on the vaccine sense. But in the reports, the WHO and CDC and, you know, it looks at the neuraminidase inhibitors and the drugs and Xofluza as well. Is there any -- I'm just curious, is there any idea at least emerging in terms of what of these drugs are better? Is the Xofluza better than the neuraminidase inhibitors or not even where they haven't moved at all? Is there anything that's any good? I mean --

And I'll ask a second question. Is there -- is the FDA looking at any -- are there any companies that are about to put out testing kits for flu that, you know, people can buy off the counter or something like this so that they would know -- they could do a swab or something -- they could know whether I need to get to the doctor because I've got to take these drugs within the first day or something like this, first day or two? And are there things like that being -- coming to the FDA?

DR. GRUBER: You know, we simply don't know because these test kits would not be regulated in the Center for Biologics, so we could actually, however, reach out to some of our colleagues in -- I think it maybe Center for Devices or CDER to see what is going on there and if something like this is developed like an at-home kit, right? Testing kit. So we're not aware because we don't really have these products under our purview.

DR. EL SAHLY: Dr. Gans.

DR. GANS: Thank you. If we're going over things that I think would be helpful to committee, I agree with like the way that we currently select our vaccines all the information that was asked for I think would be very helpful to make decisions. But I guess the most striking thing to me is that we continue to make a lot of our basis on serologic studies on the neutralization of antibodies when we know actually that there's other, better correlates of immunity, although we would probably have to change our vaccine a bit.

But anyway, I wondered if there's any efforts made to try and get something that's more cross typic that can actually go across all of these different things that we could actually make a better a prediction about where we're going with some of that instead of relying on antibodies that cause the antigenic shift. And then we're stuck with things that aren't as effective.

DR. EL SAHLY: I guess, yes, Dr. Weir.

DR. WEIR: There's -- I'm not sure I have an answer for you. There's clearly a lot of work and a lot of different areas to develop better vaccines. That's a big push throughout the government, throughout the industry, and there's a lot of money being put into it now. And so I suspect, at least I hope, that over the years that that will lead to better cross-reactive protective vaccines as well as, you know, the so-called universal vaccines.

As far as the correlates though, I'm not sure I agree with you that they're better correlates.

Unfortunately, where we are now with the existing vaccines that are mostly inactivated vaccines, antibodies are the best correlate that we have. And so that will probably be something different when a new generation of vaccines hopefully arrive that work in different ways. They probably will have different correlates and then, yes, I suspect the prediction will get harder, not easier. But anyway, I think we have a ways to go still.

DR. JANES: Dr. El Sahly, this is Holly on the phone. May I ask a question?

DR. EL SAHLY: Absolutely.

DR. JANES: Thank you. So following up on the questions around the data that are presented to the committee, I think I saw for the first time, if I remember correctly, today from the DOD indications in the phylogenetic trees as to, you know, some additional kind of characterization of the viruses and the trees, specifically with regard to whether or not they had required hospitalization of the individuals and also

whether or not there was knowledge about individuals having previously been vaccinated. So those intrigued me. And I thought, you know, if indeed those are the first time that those types of metadata are being presented to the committee, it would be helpful to understand how we ought to interpret those data, you know, and in particular looking at the hospitalization data.

Do they suggest that there's different morbidity associated with the different virus, you know, subclades and groups of viruses? And, if so, you know, was that part of the determination around the selection of the strains? And could that be made a more systematic characterization for committee meetings going forward?

DR. EL SAHLY: Yeah, Dr. Wentworth.

DR. WENTWORTH: Well, you know, we also sequence, you know, from the VE studies at the CDC. We don't put that into the -- you know, the trees I'm showing are very high level. We have trees where we

generate ourselves to look at that. If we don't see a pattern, which is typically the case, then we wouldn't bother showing. I guess, if we saw a pattern where a certain subclade was escaping vaccine-induced immunity more frequently, then we could include it.

So I think that I -- there's a lot of metadata to try to incorporate into the tree or trees. And so we can -- if that's very important to the committee, we can definitely do it. But generally what we find is it's peppered throughout the tree, and it tends to be the dominant group or subgroup of viruses that are circulating as to what breaks through the vaccine. It's the same reason they're popular. You know, it's hard to differentiate the fact that they're the dominant strain causing the epidemic, and they happen to be the thing that's also infecting the vaccinated individuals.

DR. EL SAHLY: Okay. Any comments from the room --

DR. JANES: Thank you.

DR. EL SAHLY: -- or from the attendees on the phone? Okay. So next will be the questions on which we are going to vote.

MS. HAYES: Just as a reminder, for individuals participating on the phone, you will be emailing me your responses, and then we will have those included in the tally. Thank you.

DR. EL SAHLY: So for the influenza A H1N1 component of the 2020-2021 influenza virus vaccines in the U.S., does the committee recommend an A/Guangdong-Maonan/SWL1536/2019 (H1N1) pandemic 09-like virus for egg-based vaccine, an A/Hawaii/70/2019 (H1N1) pandemic-09-like virus for cell or recombinant-based vaccine? The options are yes, no, and abstain. And Kathleen will us know when to start.

MS. HAYES: You can go ahead. Mr. Toubman and Dr. Janes, if you could email your responses now to Kathleen.hayes@fda.

DR. EL SAHLY: Do you have all the votes?

MS. HAYES: We'll just give it a couple more

minutes since I haven't received the votes via email as of yet.

DR. EL SAHLY: Holly and Shelly, would you please email Kathleen your votes?

(Pause)

DR. EL SAHLY: Shelly and Holly, are you on the phone?

MR. TOUBMAN: Yes, this is Sheldon. I did email my vote. Did you not get it by email?

DR. EL SAHLY: Kathleen did not get your votes.

MR. TOUBMAN: Okay. I'll make this really easy. The vote is yes.

DR. JANES: I voted yes as well and have emailed, but I'll do so again.

DR. EL SAHLY: Would that be sufficient or --

MS. HAYES: Thank you. I'm sure that maybe due to the firewall, they just haven't come through yet, but we'll note those votes for record. So once the votes are tallied, they'll come up on the display

and we can read them.

(Pause)

Okay. So I believe we have everyone's votes received. We'll make a note that Dr. Annunziato did not vote as an IR, and Dr. Bennink's vote was used on her microphone.

It looks like we have 15 yeses. Dr. Bennink, yes. Colonel Wiesen yes. Dr. El Sahly, yes. Dr. Beckham, yes. Dr. Chatterjee, yes. Dr. Gans, yes. Dr. Janes, yes. Dr. Kurilla, yes. Dr. Levine, yes. Dr. Meissner, yes. Dr. Offit, yes. Dr. Shane, yes. Dr. Spearman, yes. Dr. Swamy, yes. And Mr. Toubman, yes. We can move forward to question number 2.

DR. EL SAHLY: Question number 2, for the influenza A (H3N2) component of 2020-2021 influenza virus vaccine in the U.S., does the committee recommend an A/Hong Kong/2671/2019 (H3N2)-like virus for egg-based vaccines and A/Hong Kong/45/2019 (H3N2)-like for cell or recombinant-based vaccines? Yes, no, abstain on the microphone.

MS. HAYES: And those on the phone please feel free to email if I get them in time. Thank you, Dr. Janes, I received yours.

(Pause)

MS. HAYES: I've received answers for those on the phone, so I think we're ready to move forward, if you want to display the results. I'm sorry. Mr. Toubman voted yes and Dr. Janes, yes.

Again for the record, Dr. Annunziato did not vote on her microphone. Dr. Bennink's vote was entered on hers. We have all yeses once again for this question.

Dr. Bennink, yes. Colonel Wiesen, yes. Dr. El Sahly, yes. Dr. Beckham, yes. Dr. Chatterjee, yes. Dr. Gans, yes. Dr. Janes, yes. Dr. Kurilla, yes. Dr. Levine, yes. Dr. Meissner, yes. Dr. Offit, yes. Dr. Shane, yes. Dr. Spearman, yes. Dr. Swamy, yes. And Mr. Toubman, yes. Next question, please.

DR. EL SAHLY: For the influenza B component of the 2020-2021 trivalent influenza virus vaccine in

the U.S., does the committee recommend inclusion of a B/Washington/02/2019-like virus B/Victoria lineage?

MS. HAYES: I received the results for Dr. Janes. Mr. Toubman, I haven't received your vote yet. Did you want to just say it over the phone and I'll keep your email for record? Oh, I just received it. Thank you. So we should have all responses at this point in time.

Okay. This question has passed. It looks like we have 15 yes votes. Dr. Bennink, yes. Colonel Wiesen, yes. Dr. El Sahly, yes. Dr. Beckham, yes. Dr. Chatterjee, yes. Dr. Gans, yes. Dr. Janes, yes. Dr. Kurilla, yes. Dr. Levine, yes. Dr. Meissner, yes. Dr. Offit, yes. Dr. Shane, yes. Dr. Spearman, yes. Dr. Swamy, yes. Mr. Toubman, yes.

MR. TOUBMAN: Yes. Hi, I voted yes.

MS. HAYES: Yes, thank you. Next question.

DR. EL SAHLY: For quadrivalent 2020-2021 influenza vaccines in the U.S., does the committee recommend inclusion of a B/Phuket/3037/2013-like virus

B/Yamagata lineage as the second influenza B strain in the vaccine?

MS. HAYES: We have the response for Dr. Janes. Mr. Toubman, I'm sure your email is still coming through but feel free to vocalize your response, and I'll note your emails for record.

MR. TOUBMAN: Yes, the vote is yes. Thank you.

MS. HAYES: Thank you. We should have all responses at this point in time. Again, we have 15 yeses. Dr. Bennink, yes. Colonel Wiesen, yes. Dr. El Sahly, yes. Dr. Beckham, yes. Dr. Chatterjee, yes. Dr. Gans, yes. Dr. Janes, yes. Dr. Kurilla, yes. Dr. Levine, yes. Dr. Meissner, yes. Dr. Offit, yes. Dr. Shane, yes. Dr. Spearman, yes. Dr. Swamy, yes. And Mr. Toubman, yes. This should conclude the voting for topic one.

DR. EL SAHLY: All right. Mission one accomplished.

MR. TOUBMAN: Can I ask a question? This is

Sheldon Toubman. Can I ask one question?

DR. EL SAHLY: Yes, of course.

MR. TOUBMAN: So I've been on this committee for three-and-a-half years, and, of course, I'm the person who really doesn't know anything. I barely understand what's being talked about. I try to follow it.

But it does seem that -- my question is going to be about the selection of a third A instead of two Bs, the question raised earlier. It does seem that whatever the WHO suggests is always adopted unanimously. And I don't think there's anything wrong with that because, obviously, they seem to be preeminent world public health organization with all the appropriate expertise. It does seem, however, that that is the result. Whatever WHO says becomes what's adopted by the FDA.

And if that's going to continue to be the case, maybe this question isn't really relevant. But if it might not always be the case, I do have this

question about why there wouldn't be consideration of having, in a quadrivalent, having three As if the conclusion after looking at the evidence is that actually that would probably be the most protective for the coming season. And yet, I heard the -- I don't know who asked the question because I'm on the phone, so I couldn't really hear or see very well.

But somebody asked the question is could we do that. And I couldn't understand the answer very well, but it seemed to be that the answer was that something about licensing would be difficult for the manufacturers to do that. And I guess my question is, if that is an obstacle, is that something that should be looked at so that, in the future there might be an option to -- for the committee to say, you know, actually, the best thing this particular year would actually to have three under A and not for the quadrivalent as opposed to having a second B? Is that something worth looking at, whether it's something to be done there to make that a possibility?

DR. EL SAHLY: I can begin the answer. I think, well -- Dr. Weir.

DR. WEIR: I can elaborate a little bit on what I said earlier. Any sort of changes in formulation do have to go through the licensing procedure, and a company would have to come to the agency with their proposal and have data to support that. Off the top of my head, I could say you'd probably be looking for things like would the inclusion of another A impact the response to the ones already in there. Those would just be sort of the basic things one would do.

But the simple answer is that it would change the license. I don't know how difficult it would be. It would clearly be something that I doubt one company would take on their own because, again, they would be doing that without any WHO recommendation. Their license would kind of be in a strange position. It could be a public health question that is bigger than what this committee addresses.

I mean, these may be the type of studies that, you know, someone else, NIH for example, could undertake, you know. Would those type of vaccine formulations be of benefit, and, if that sort of data were generated, maybe it would spark interest in changing that sort of recommendation. And then the companies could follow. So anyway. Marion?

DR. GRUBER: I just wanted to amplify a little bit. I mean, Jerry's absolutely right. What we would need is what we usually refer to as supplemental biologic license application, much like we have done when we licensed quadrivalent influenza vaccines. So you know, the manufacturer would do the clinical studies, probably immunogenicity studies, to really look at, you know, a potential interference of the different strains.

And so I think, you know, from a regulatory perspective, it's doable, but I think it raises a lot of other very complex and difficult questions that we need to answer. And I think one of the questions is --

and I think that maybe toward the vaccine manufacturers factors. I mean, we've heard, you know, the strenuous conditions and the timelines out of which these vaccines are made now. So let's say adding now a third, let's say, H1N1 or, you know -- what would this really mean in terms of manufacturing, manufacturing capacity, the logistics of, you know, getting the candidate virus, et cetera, et cetera?

I think it adds another layer of complexity and poses questions regarding timely availability, not only about the vaccines at the end, but also necessary reagents that need to be made and available to really measure the strengths and potency of these products. So I think it's an important but a very complex discussion. And I don't think there's just one easy answer for that.

DR. EL SAHLY: Okay.

MR. TOUBMAN: Thank you for the answer. I guess the question is whether -- is this the, no pun intended, chicken or egg in the sense that does WHO

always, for the quadrivalent, always recommend two Bs because of this problem that you're identifying, this significant regulatory obstacle? And so, in fact, that's why they would never go there. Is that what's going on? Because if it's going on or partly going on, then it does seem it's a conversation worth having.

DR. EL SAHLY: Clinical research data would be needed, but it may be where the field may have to go at one point. Dr. Meissner?

DR. MEISSNER: Well, I was just going to make the comment for Dr. Weir and Dr. Gruber to respond. I mean, one way around it would be to make a second vaccine. So that would be the traditional four-valent and then, as we had in 2009 for the pandemic strain, another vaccine. And so it would mean people getting immunized twice or with two different vaccines, but that might be an option to address this interesting issue.

DR. EL SAHLY: We have Dr. Chatterjee and then Dr. Bennink.

DR. CHATTERJEE: I have a question for our FDA colleagues as well. With regard to concomitant administration of other vaccines, primarily for children because they're receiving a lot of other vaccines at the same time, would those studies be required as well?

DR. GRUBER: It's always good to have this data. It would not be a requirement to licensure to have these data on concomitant vaccine administration at the time that, you know, presumably we would license a new formulation. But usually manufactures do really acquire those data, sometimes, you know, post-licensure.

DR. EL SAHLY: Dr. Bennink.

DR. BENNINK: Yeah. I think it's obvious, but the real solution, if possible, is a universal vaccine. And I think that's where all the push and drive is. And when that comes about, then the companies will be, you know, really driving to license that.

[END OF TOPIC I OPEN SESSION]