FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
171st Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN PUBLIC MEETING

Web-Conference
Silver Spring, Maryland 20993

March 3, 2022

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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Paula Annunziato, M.D.	Merck
Adam Berger, Ph.D.	National Institutes of Health
Henry Bernstein, D.O., MHCM, FAAP	Zucker School of Medicine and Cohen Children's Medical Center
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
David Kim, M.D., M.S., M.H.A.	U.S. Department of Health and Human Services
Arnold Monto, M.D.	University of Michigan
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine & Children's Healthcare of Atlanta
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TEMPORARY VOTING MEMBERS	
COL Douglas Badzik, M.D, M.P.H.	Office of Secretary of Defense Health Affairs
David Wentworth, Ph.D. (Non-Voting)	Centers for Disease Control and Prevention
SPEAKERS AND GUEST SPEAKERS	
CAPT Lisa Groshskopf, M.D, M.P.H.	Centers for Disease Control and Prevention
Beverly Taylor, Ph.D.	Sequirus
Courtney Gustin, PH, RS, MH.	Armed Forces Health Surveillance Division

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Jerry Weir, Ph.D.	Food and Drug Administration
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Mr. Michael Kawczynski	Food and Drug Administration

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OPENING REMARKS: CALL TO ORDER, INTRODUCTION OF COMMITTEE

MR. MICHAEL KAWCZYNSKI: Good morning, and welcome to the 171st meeting of the Vaccines and Related Biological Products Advisory Committee meeting. This one's specializing on influenza. I'm Mike Kawczynski, and I will be kicking things off this morning. This is a live virtual event, so we do anticipate every once in a while that there may be a little glitch here and there, not to worry. This meeting is being recorded and broadcast live on YouTube. So, if we do run into a technical issue, we will take a momentary break and come back, get it fixed, and make sure that you don't miss any of this wonderful information being shared today.

With that, I'd like to hand it over to our chair Dr. Hana El Sahly. El Sahly, do you have a second? We'll let you turn your camera on and take it away.

DR. EL SAHLY: Good morning, everyone. I want

to welcome the Committee members, the participants, and the public to the 171st meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to remind all our members to use the raise your hand function whenever you have a question or comment to make, and we will call on your name where it appears. And with that, I want to turn it over to Dr. Atreya. Dr. Prabha Atreya is the Designated Federal Officer for the meeting today.

She'll make some administrative announcements, do the roll call, and the conflict of interest. Dr. Atreya?

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICTS OF INTEREST STATEMENT

DR. PRABHAKARA ATREYA: Thank you, Dr. El Sahly. Good morning, everyone. This is Prabha Atreya, and it is my great honor to serve as the Designated Federal Officer, that is DFO, for today's 171st Vaccines and Related Biological Products Advisory

Committee meeting.

On behalf of the FDA, the Center for Biologics Evaluation and Research, and the vaccines advisory committee, I would like to welcome everyone for today's virtual meeting. Today the Committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2022/2023 influenza season. The meeting and the topic were announced in the Federal Registered Notice that was published on January 25th, 2022.

I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great support team we have at FDA in preparing for this meeting. Ms. Christina Vert is my backup co-DFO providing excellent administrative support in all aspects of preparing for this meeting. She will also be participating in conducting the voting process later in the day.

Other staff members who contributed are Ms. Joanne Lipkind, Ms. Lisa Wheeler, Ms. Karen Thomas who

provided great support in preparing for this meeting. I would also like to express CBER's sincere appreciation to Mr. Mike Kawczynski in facilitating the meeting today. And also, a big shout out to many FDA staff working hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one, like all the previous virtual VRBPAC meetings.

Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at FDAOMA@FDA.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles and Ms. Erica Denham.

We will begin today's meeting by taking a formal roll call for the Committee members and the temporary members who are participating. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name. And when finished, you can turn off your camera so we can proceed to the next person.

Please see the member roster slides in which we will begin with the Chair. Mike, next slide, please. Dr. El Sahly, can we start with you, please?

DR. HANA EL SAHLY: Morning, everyone. Hana El Sahly, professor of molecular virology and microbiology at Baylor College of Medicine. My line of work is adult infectious diseases, and my research focuses on clinical vaccine development.

DR. PRABHAKARA ATREYA: Thank you. Dr. Annunziato.

DR. PAULA ANNUNZIATO: Good morning. My name is Paula Annunziato. I lead vaccine clinical development at Merck, and I'm here today as the non-voting industry representative.

DR. PRABHAKARA ATREYA: Thank you. Dr. Berger.

DR. ADAM BERGER: Hi, I'm Adam Berger, the director of the division of clinical and healthcare research policy in the Office of Science Policy, which is part of the director's office of NIH.

DR. PRABHAKARA ATREYA: Thank you. Dr. Bernstein.

DR. HENRY BERNSTEIN: Good morning. I am Hank Bernstein. I'm a professor of pediatrics at Zucker

School of Medicine in New York.

DR. PRABHAKARA ATREYA: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning, everyone. My name is Archana Chatterjee. I am the dean at the Chicago Medical School and vice president for Medical Affairs at Rosalind Franklin University in Chicago. My area of expertise is in pediatric infectious diseases with a concentration in vaccines. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, we have Captain Amanda Cohn.

CAPT. AMANDA COHN: Good morning, everyone. I'm Dr. Amanda Cohn. I'm a pediatrician at the Centers for Disease Control and Prevention with expertise in vaccines and public health.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Holly Janes. Maybe she will join. Oh, you got it. Okay, great. Go ahead, Holly. We can't hear you. Still can't hear you.

MR. MICHAEL KAWCZYNSKI: There you go. Go

ahead, Holly. I unmuted you.

DR. HOLLY JANES: Thank you. I'm a professor at the Fred Hutchinson Cancer Research Center. My training is in biostatistics, and I work in vaccine trial design and evaluation. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next up, Dr. David Kim.

MR. MICHAEL KAWCZYNSKI: Dr. Kim's not with us, yet. He's still logging in. So, let's jump onto the next one, please.

DR. PRABHAKARA ATREYA: Okay, thank you. Dr. Monto.

DR. ARNOLD MONTO: I'm Arnold Monto. I am now Professor Emeritus in epidemiology and public health at the University of Michigan, and I work on influenza and coronaviruses, both evaluation of the vaccines and examining vaccine effectiveness.

DR. PRABHAKARA ATREYA: Thank you. Dr. Jay Portnoy.

DR. PAUL OFFIT: Oops.

DR. PRABHAKARA ATREYA: Sorry. Dr. Paul

Offit.

DR. PAUL OFFIT: Yeah, good morning. My name's Paul Offit. I'm a professor of pediatrics at the Children's Hospital Philadelphia and the University of Pennsylvania School of Medicine. My expertise in the area of vaccines.

DR. PRABHAKARA ATREYA: Thank you, Dr. Offit. Next, Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you. We wouldn't want to miss Dr. Offit's introduction. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri Kansas City School of Medicine. I'm an allergist/immunologist at Children's Mercy Hospital in Kansas City.

DR. PRABHAKARA ATREYA: Thank you. Next, we will do the roll call of our -- introduce the temporary voting and non-voting members. Colonel Douglas Badzik -- Andrea Shane, I'm sorry. Go ahead, Dr. Shane.

DR. ANDREA SHANE: Good morning, everyone. I'm Dr. Andrea Shane. I'm a professor of pediatric infectious diseases at Emory University School of

Medicine and Children's Healthcare of Atlanta, and my area of expertise is pediatric vaccines and epidemiology. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, we will introduce Dr. Badzik. Can't hear you, Dr. Badzik.

MR. MICHAEL KAWCZYNSKI: Yep, you got to unmute yourself, sir.

DR. DOUGLAS BADZIK: All right. Sorry about that, everyone. Dr. Doug Badzik. I am the director of preventative medicine for the Office of the Secretary of Defense for Health Affairs, and I am a preventative medicine physician.

DR. PRABHAKARA ATREYA: Thank you. Next, our non-voting member David Wentworth.

DR. DAVID WENTWORTH: Good day, everybody. My name is David Wentworth, and I am with the Centers for Disease Control. I'm the branch chief for the Virology Surveillance and Diagnostics Branch in the Influenza Division. And I'm also our WHO Collaborating Center director. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, I

would like to introduce the FDA staff. First, I would like to introduce Dr. Peter Marks, the director of the Center for Biologics and Jerry Weir who is also involved. Dr. Marks, can you address the Committee?

DR. PETER MARKS: Hey, good morning. Thanks very much. Well, I'll take this opportunity to just welcome everyone and to thank everyone for taking the time today. Despite all of what we've been through with coronavirus in the past two years, we still have to take the threat of influenza very seriously. And so I greatly appreciate your participation today. Thanks very much, and we look forward to a good discussion today. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Marks. Now I will proceed with reading of the Conflict of Interest statement for the record. Okay, the Food and Drug Administration, FDA, is convening virtually today, March 3rd, 2022. The 171st 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 voting chair

for today's meeting.

The Committee today will meet in open session and make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2022 to 2023 Northern Hemisphere influenza season. This topic is determined to be a particular matter involving specific parties. With the exception of the industry representative members, all standing and temporary members of the VRBPAC are appointed as special government employees (SGEs) or regular government employees (RGEs) from other government agencies and are subjected to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with the federal Ethics and Conflict of Interest laws, including but not limited to, 18 U.S. Code Section 208 is being provided to participants in today's meeting and to the public. Related to the discussions at the meeting, all members, regular government members, and the special government employees consulted for this Committee have been

screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purpose of 18 U.S. Code 208, their employer.

These interests may include investments, consulting, expert witness testimony, contracts and grants, corporate research and development agreements or CRADAs, teaching, speaking, writing, patents and royalties, and then finally employment. These may include interests such as current or under negotiation. FDA has determined that all members of this advisory committee -- both the regular and temporary members -- are in compliance with federal Ethics and Conflicts of Interest laws.

Under 18 U.S. Code Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential for the conflict of interest created by the interest

involved or when the interest of the particular government employee who is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda, and all financial interests reported by Committee members and consultants, no conflicts of interest waivers have been issued under 18 U.S. Code 208 in connection with this meeting today. We have consultant Dr. Douglas Badzik serving as the DoD representative and a temporary voting member. Colonel Douglas Badzik is a regular government employee serving as a director of preventative medicine in the Office of the Assistant Secretary of Defense Health Affairs and Health Readiness Policy and Oversight in Virginia.

He currently serves as the lead preventative medicine policy advisor for the deputy assistant secretary for defense for Health Readiness Policy and Oversight. Douglas Badzik has been screened for conflicts of interest and cleared to participate in today's meeting as a temporary voting member, and he's

authorized to participate in Committee discussions.

We also have Dr. David Wentworth serving as a temporary non-voting member and speaker for this meeting. Dr. David Wentworth is employed by the Centers for Disease Control and Prevention as the chief of the Virology Surveillance and Diagnostic Branch in the Influenza Virus Division. He's an internationally known expert in influenza virus epidemiology, worldwide influenza disease burden, and influenza virus vaccines.

Dr. Wentworth is a regular government employee at CDC and has been screened for conflicts of interest and cleared to participate both as a speaker and as a non-voting member of today's meeting. As a speaker and temporary non-voting member, Dr. David Wentworth is not only allowed to respond to the clarifying questions from the Committee members but also is authorized to participate in Committee discussions in general. However, he's not authorized to participate in the Committee voting process.

Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting.

Industry representatives are not appointed as special government employees and serve as non-voting members of the Committee. Industry representatives act on the behalf of all regulated industry and bring general industry perspective to the Committee. They are not screened and do not participate in any closed sessions, if held, and do not have voting privileges.

Dr. Jay Portnoy 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, and they are voting members of the Committee.

Disclosures of the conflict of interest for speakers and guest speakers follow all applicable federal laws, regulations, and FDA guidance. The guest speakers for this meeting today are the following. Dr. Lisa Groshskopf, the chief medical officer in the Virology and Prevention Branch at CDC is participating as a guest speaker.

Also Dr. Courtney Gustin is a respiratory

focus area lead in the Global Emerging Instruction Surveillance Branch in the Department of Defense. These speakers have been screened for conflicts of interest and cleared to participate as speakers for today's meeting.

As guest speakers, Dr. Groshskopf and Dr. Gustin are allowed to respond to clarifying questions from the Committee members following their presentation. However, they are not authorized to participate in the Committee discussions or to participate in the Committee voting process.

Dr. Beverly Taylor is the head of the Influenza Technical Affairs and Pandemic Readiness within the Technical Operations at Speke. She is serving as a guest speaker from the industry to provide flu vaccine manufacturers' perspective to the Committee. Dr. Taylor is allowed to respond to clarifying questions from the Committee members following her presentation. However, she's not authorized to participate in Committee discussions or in the voting process.

FDA encourages all meeting participants -- including the open public hearing speakers -- to advise the Committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors.

We would like to remind standing and temporary members that, if the discussions involve any of the products or firms that are not already on the agenda for which an FDA participant has a personal and imputed financial interest, the participants need to inform the DFO and exclude themselves from the discussion and the exclusion will be noted for the record. This concludes the reading of the Conflicts of Interest statement for the public record.

At this time, I would like to hand over the meeting to our Chair, Dr. El Sahly, to continue the meeting. Thank you all for your attention. Hana, take it away.

INTRODUCTION - INFLUENZA VIRUS VACCINE STRAIN SELECTION 2022-2023 NORTHERN HEMISPHERE

DR. HANA EL SAHLY: Thank you, Dr. Atreya. Next, I would like to introduce Dr. Jerry Weir. Dr. Jerry Weir is the director of the Division of Viral Products at the Office of Vaccines Research and Review. Dr. Weir will do an introduction on the meeting today.

DR. JERRY WEIR: Hi. Thank you, and good morning. I'm Jerry Weir, and I'm the director of the Division of Viral Products at CBER. And I'm going to provide a brief introduction, remind everybody why we're here today, and preview the questions that the Committee will vote on. So, we'll go right into it. Shouldn't take very long.

So, the purpose of today's VRBPAC discussion is to review influenza surveillance and epidemiology data, genetic and antigenic characteristics of recent virus isolates, virological response to current vaccines, and the availability of candidate vaccine strains and reagents.

After that review and discussion, the Committee will make recommendations for the strains of Influenza A, both H1N1 and H3N2; and the B viruses to be included in the 2022/2023 influenza vaccines licensed for use in the United States. As you'll see, we start out, of course, with looking at the recommendations the World Health Organization has made. But it's the responsibility of every national regulatory authority to make recommendations for vaccines in their country, and that is the role of the VRBPAC in this process.

So, the type of analysis that you will see today include the epidemiology of circulating strains. This comes from surveillance data from the U.S. and around the world. You'll also hear extensive antigenic relationships among contemporary viruses and candidate vaccine strains. The type of techniques will include hemagglutination inhibition, or HI, microneutralization tests using post-infection ferret sera. You'll also hear about HI and microneutralization tests using panels with sera from humans receiving recent influenza

vaccines. They'll also be presentations on antigenic cartography and phylogenetic analysis of HA and NA genes as well as some work on vaccine effectiveness.

Okay, to preview where we are, about a year ago -- almost exactly a year ago -- there was a WHO recommendation for the current influenza season, the one we're in now, 2021/2022. The WHO recommendation was made on February 26th. This VRBPAC met about a week later on March 5th. At that time, the recommendation for vaccines in the U.S. included, for Influenza A(H1N1), an A/Victoria/2570/2019 pandemic-like virus for egg-based vaccines; and an A/Wisconsin/588/2019 pandemic-like virus for cell and recombinant vaccines. For the H3N2 component of the vaccines, the recommendation was for an A/Cambodia/e0826360/2020 H3N2-like virus. And all trivalent and quadrivalent vaccines were recommended to have a B/Washington/02/2019-like virus from the B/Victoria strain. The Influenza B component as a second B component for quadrivalent vaccines was recommended to contain a B/Phuket/3073/2013-like virus.

Okay, so last week -- I think it was last week -- February 25th, the WHO made a recommendation for the upcoming season, in other words, next winter Northern Hemisphere season 2022/2023. The WHO made the following recommendation. For Influenza A(H1N1), the WHO recommended an A/Victoria/2570/2019 H1N1 virus for egg-based vaccines, and they recommended an A/Wisconsin/588/2019 pandemic09-like virus for cell and recombinant vaccines. For the H3N2 component, the Committee recommended an A/Darwin/9/2021 H3N2-like virus for egg-based vaccines and an A/Darwin/6/2021-like virus for cell and recombinant vaccines. I'm sure you'll fill more in the presentations about what was behind the different recommendations for egg and cell vaccines.

The Influenza B component for both quadrivalent and trivalent vaccines, the recommendation was a B/Austria/1359417/2021-like virus from the B/Victoria lineage, and for quadrivalent vaccines containing the above three virus strains, the recommendation for the fourth strain was a

B/Phuket/3073/2013-like virus from the Yamagata B virus lineage.

So, the Committee today will discuss, as I said, which influenza strain should be recommended for the antigenic composition for the 2022/2023 influenza virus vaccines in the U.S.

As always, the Committee will have several options, but the way we do this to try to make it simpler and to streamline it a little bit, the options will be to start with the WHO recommendations, review those, vote on those, and, if the Committee wants to consider something else, they can recommend alternative strains.

For example, for the H1N1 components, we can start with -- the Committee can recommend the A/Victoria strain for the egg-based vaccines and the A/Wisconsin strain for cell and recombinant-based vaccines. Or after hearing the data and reviewing the data, the Committee could recommend an alternative H1N1 candidate vaccine strains. Similarly, for the H3N2, the Committee can recommend the A/Darwin/9 or the

A/Darwin/6 strains recommended by the WHO, or after hearing the data, they can recommend an alternative H3N2 strain.

For B, for trivalent and quadrivalent vaccines the Committee can consider a B/Austria strain that the WHO recommended, or they can recommend a different candidate vaccine virus from the same B/Victoria lineage or even recommend a strain from the B/Yamagata lineage. And, finally, for the second B strain to be included, the Committee can recommend a B/Phuket-like virus as recommended or recommend alternative strains for consideration.

So, the voting questions, again, to streamline it, we're going to take four votes: one for H1N1, one for H3N2, one for the Influenza B component that is for trivalent and quadrivalent vaccines, and then the fourth vote will be for the second B strain for quadrivalent vaccines. Again, we'll start out with the voting questions. We'll start out with the WHO recommendations, and then we'll go from there. If the Committee recommends that these be the selection, then

that will be the vote. If not, then we would reconsider and come up with something else.

So, I won't read them all again, they're the same things I just went through with the options. For the Influenza A, we'll consider the A/Victoria and A/Wisconsin strains together. And for the H3N2, we'll consider the two Darwin strains recommended for egg-based vaccines and cell recombinant-based vaccines together. So, I think I'll stop there, and if there are any questions, otherwise we can proceed with the presentation.

Q AND A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Weir. I would like to invite the Committee to ask questions or provide comments on the presentation by Dr. Weir, and we will begin by Dr. Portnoy. Dr. Portnoy, please unmute yourself and turn your camera to ask your question.

DR. JAY PORTNOY: Thank you, Dr. Weir. I

guess my question is you've got egg-based vaccines and you've also got cellular recombinant vaccines. When somebody gets a vaccine, do they get only egg or only recombinant or are they mixed together? Or how is that done? And if you get only the egg vaccines, you're not getting the strains from the recombinant vaccines. Why would they be different? Can you explain that, please?

DR. JERRY WEIR: Okay, so we have lots of licensed vaccine manufacturers. They are either, egg-based vaccines. That's still the majority of the vaccines. We have one cell-based vaccine, and we have one recombinant-based vaccine. So, there is no mixing of egg and cell within a vaccine. Like I said, for a manufacturer that makes an egg-based vaccine, all the strains will be egg-based vaccines. What was the second part of that again?

Oh, they get slightly different strains but, yes, all of those strains are supposed to be antigenically similar even though some are better growers and better suited for an egg-based vaccine, or some are better suited for cell-recombinant vaccines.

But antigenically they should be the same or very similar.

DR. JAY PORTNOY: Okay, great. Thank you.

DR. HANA EL SAHLY: Dr. Weir, I have a question just to tap into your institutional memory here. Did the Committee ever recommend an alternative that was (audio skip)?

DR. JERRY WEIR: Okay. No, I don't think so. But it can happen, and there have been examples in other countries where that happens. I will say from a practical matter, you might remember that the U.S. has a lot of representation at the WHO meeting. Both the CDC is represented; we at CBER are represented. Saint Jude is represented. So, it's probably unlikely because our views for the U.S. are taken into consideration, but it can happen. And again, influenza viruses tend to circulate and be global, but every once in a while, some area of the world will be a little different from something else. So that is why we have to consider it.

DR. HANA EL SAHLY: Great. I see no hands

raised. Thank you, Dr. Weir.

DR. JERRY WEIR: Thank you.

U.S. SURVEILLANCE - INFLUENZA ACTIVITY AND VE UPDATE

DR. HANA EL SAHLY: Our next presentation is by (audio skip) Groshskopf, the associate chief for Policy and Liaison Activities Influenza Division at the CDC. Dr. Groshskopf will give us the U.S. surveillance update. Dr. Groshskopf.

MR. MICHAEL KAWCZYNSKI: Dr. Groshskopf, let me make sure we get you -- hold on, we didn't hear you yet. Let me make sure you're unmuted.

DR. LISA GROSHSKOPF: I am unmuted now. Thank you.

MR. MICHAEL KAWCZYNSKI: There we go. Now you got it.

DR. LISA GROSHSKOPF: Okay. Thanks very much. I'm going to be shutting my camera off during the presentation, but I'll bring it back at the end. So, I'll be presenting a brief update of CDC domestic

influenza surveillance as well as a preliminary interim estimate of vaccine effectiveness for this season. We're going to start with surveillance, and I'm going to be presenting a number of slides from the most recent CDC FluView report and this comes out every week. It will be updated next tomorrow.

The most recent report is for Week 7 which is the week ending February 19th, 2022. Before starting, I just want to thank the members listed here of our Influenza Division Domestic Surveillance Team of whom I'd just like to acknowledge for the amazing work they do on a regular basis.

So, we're going to start with virologic surveillance today. This first slide summarizes results of influenza-positive test results reported to CDC on a weekly basis from surveillance laboratories located throughout the United States.

These laboratories include two basic categories. We have clinical laboratories shown on the left, and public health laboratories shown on the right. We do get slightly different data from each of

them. In general, the clinical laboratories might not, for example, perform type and subtype or lineage testing, so we generally end up with fewer colors on that graph. For the clinical labs, they generally do perform type and subtype testing.

Looking first at the graph on the left, which is for the clinical laboratories, the bars represent the number of isolates. Yellow represents Influenza A. Green, which is very small in quantity, they represent Influenza B. And the black line represents the percent of respiratory specimens testing positive. The percent of respiratory specimens testing positive peaked initially for the season at Week 50, so approximately mid-December at about six percent and then declined over late December and January to a low of about two percent by Week 2 of the year.

Since that time, the percent of specimens testing positive have begun to creep up again, and it's increased over the past couple of weeks by 4.2 percent. The previous week was three percent. Again, as you can see, most of the graph is yellow. We have most

positive specimens testing for Influenza A as denoted by the yellow bars.

For the public health laboratory figure on the right, this shows that the red color represents H3N2. The majority of the viruses subtyped -- and those are in red -- are H3N2 viruses.

Next, we're going to move on to influenza-like illness surveillance. One point to note about the slides that follow that discuss illnesses or hospitalizations or deaths, some of these surveillance systems track laboratory-confirmed influenza outcomes and some of them don't. So, I'm going to try to be careful to point out which do and which don't. This is influenza-like illness activity. This is from ILINet, and this is a network of providers who report weekly to CDC the percent of outpatient visits that were positive for -- that were for the purpose of influenza-like illness or ILI.

The system uses a symptom-based or syndromic definition and not laboratory-confirmed flu. So not everything you see here is going to be flu, but it is

useful for tracking influenza-like illness activity, which is a proxy for influenza over the course of a season.

There are a number of seasons represented in this graph. The current season is represented by the line with the superimposed red triangles. For our current 2021/2022 season, we had ILI activity reported to this system peak in mid to late December. It has since declined below epidemic threshold. There's a slight uptick in the most recent week that's just barely there, and we'll have to see where that goes over the next number of weeks.

So, next, there are two slides that summarize hospitalization data from two different reporting systems. This first one is for FluSurv-NET, and this consists of cumulative hospitalization rate data. They are reported on a weekly basis. They are summarized in this slide as cumulative rates. So, we expect that the line is going to go up over the course of time because we suspect that there'll be more hospitalizations over the course of time. It's not presented here as a week-

by-week number.

Several seasons, again, are represented in this figure. The current 2021/'22 season is represented by the orange line that's rather close to the x-axis. The previous 2020/'21 season is represented by the lower line which hugs the x-axis. As we all know, last season was relatively notable for very low influenza activity. We do have somewhat more during this season.

Overall, cumulative hospitalization rates are tracking higher than they were during the 2021 season but are still lower than the previous four seasons that are also represented in this chart. Those are 2016/'17 through 2019/'20. Cumulative hospitalization rates thus far for this season is 4.9 per 100,000.

This next one also summarizes hospitalization data. This is from a system that's relatively newer to the weekly FluView report. User data from HHS Protect, and they also summarize hospitalizations associated with laboratory-confirmed influenza as did the last slide of FluSurv-NET data. To this system, hospitals

report the number of patients admitted with laboratory-confirmed influenza each week. Unlike the FluSurv-NET data on the last slide, this slide depicts hospitalizations by week rather than cumulative rates. So, you don't see a progressive incline upward over the course of time. Similarly, to previous slides, we have calendar week on the x-axis.

As of February 2nd, 2022, hospitals are now required to report laboratory-confirmed influenza hospitalizations to this system. Prior to that date, reporting was optional. So, something to keep in mind when you look at the slides. The peak reporting week here was Week 52, the last week of 2021, for which 2,616 hospitalizations were reported. This was, however, before reporting became mandatory. So, we can just keep that in mind.

For the most current week, Week 7, or the week ending February 19th, 1,420 such hospitalizations reported. You can see a bit of an increase over the last several weeks towards the right-hand side of that graph. And this is something, of course, we'll be

continuing to follow. For the total cumulative number of hospitalizations reported to the system was 5,066. But, again, that caveat was that reporting was not yet mandatory for much of this period.

Our last surveillance system slide summarizes mortality, and these data come from two different systems which have some different characteristics, so we'll briefly summarize those. The slide on the left shows mortality data from the National Center for Health Statistics Mortality Surveillance System which collects and reports weekly the percent of deaths attributed on death certificates to pneumonia and influenza. So, these are not laboratory-confirmed flu deaths.

Since early 2020, this system has also tracked deaths attributed to COVID-19. The red line that snakes across the graph denotes the percent of deaths attributed to all of these causes, while the yellow areas represent pneumonia and influenza specifically, and the blue COVID-19 specifically. For the current reporting week, 22.6 percent of deaths were attributed

to pneumonia, influenza, or COVID-19.

The right-hand graph summarizes pediatric mortality associated with laboratory-confirmed influenza, which has been reportable in the United States since 2004. And these are deaths that are associated with laboratory-confirmed disease. For the last season 2020/2021, one pediatric death was reported. Thus far, for this season, 2021/'22, a total of six deaths have been reported.

So just a brief summary of some points from domestic surveillance as of Week 7. The most recent reporting week, 4.2 percent of specimens submitted to clinical laboratories were positive after having peaked at about six percent initially at Week 50 and declining to two percent. We are seeing an uptick in more recent weeks. We're currently at 4.2 up from 3 percent the previous week, and we will get new reporting data on that tomorrow.

Most of the specimens that are subtyped in virologic surveillances are H3N2 viruses. Influenza, overall in the country, activity is sporadic, but it is

actually increasing in some parts of the country and is not uniform across the United States but continues to be sporadic and increasing in some parts of the country. The cumulative hospitalization rates, one of our indexes of severe illness -- FluSurv-NET -- is higher for that of the entire 2021 season but lower than that observed at this time during the four seasons preceding the COVID-19 pandemic.

So, moving on next are some slides from two sources just to provide some idea of preliminary VE for the season. This first part is just one slide, and the second part's a bit longer. The second part will summarize what we usually cover in this meeting every year, which is a preliminary estimate of VE from the U.S. Flu VE Network. This first slide, there's just one that summarizes some information regarding an outbreak associated with the university campus earlier this year.

So, before presenting the Flu VE Network, just to summarize this slide, there is a period of time in October/November during which the overall activity in

the United States was low but where influenza outbreaks had been reported on several U.S. university campuses even though the overall activity in the country was on the low side.

In this particular outbreak, a large number of influenza positives were detected by multiplex testing in a university campus. Among these, 519, or 20 percent, out of 2,882 ill students that were tested at campus health service were Influenza A positive. Direct sequencing of these viruses from clinical specimens identified Influenza A(H3N2) HA subclade 3c.2a1b group 2a.2.

The overall efficacy in this population over the course of this outbreak was zero. Overall, the rates of vaccination were similar for both groups, the infected and the non-infected. There were more details about this that were published in an MMWR earlier in the fall. So, this provided an early index of VE while overall activity was still low.

So, moving onto the Flu VE Network. Last year at this time when we spoke, we were in a period of

pretty much historically low influenza activity, and there was not enough information with which to get a VE estimate last season. We are seeing a bit more activity this season as you can see from surveillance and are able to have a preliminary VE estimate. There are some caveats associated which we'll go over at the end, but we'll present what we have thus far.

So, this estimate comes from the U.S. Flu VE Network, which is a network of currently seven sites that provides estimates of influenza vaccine effectiveness using an observational test-negative case-control design each season, and the sites are denoted here on this map. Sorry, I'm having a little trouble changing slides here. I hope you can see it; I can't. So, I'm going to back up. I think this is a network issue. Just give me one second. Okay, so we have our map. Good, okay. So --

DR. HANA EL SAHLY: We now have interim results slides. Is that what you want?

DR. LISA GROSHSKOPF: Perfect. Okay, so now we match. Thank you very much. I appreciate that.

So, this network enrolled outpatient aged six months or older who have acute respiratory illness with cough of less than or equal to seven days duration. The data presented on these slides represent enrollment between October 4th and January 27th. So, they're relatively current, about a month back in terms of when they were summarized. The network, again, uses a test-negative case-controlled design in which the odds of vaccination among the influenza RT-PCR positive cases is compared to (inaudible) of the vaccination among influenza RT-PCR negative controls.

So, all of these patients present to an outpatient facility with respiratory illness, and they're sorted into cases or controls based on their test status, which is done by RT-PCR. For these preliminary analyses, vaccination status is defined by receipt of at least one dose of any 2021/'22 seasonal flu vaccine according to medical records, immunization registries, and/or self-report. As these data are completed and we get closer to the end of the season and beyond, those statuses are confirmed. But in some

cases this year, we don't have confirmed vaccination data.

And VE is calculated in one minus the adjusted odds ratio times 100 percent, and models that are used to do this are adjusted for several potential compounding factors including study site, age, and month of illness onset.

So, for the periods of time that we have, which is through January 22nd, 2022, a total of 2,758 were enrolled as of that point: 2,611 or 95 percent were flu negative, 147 or 5 percent were flu positive. Among all the subtyped viruses, these were A(H3N2). All sequenced viruses belonged to a single genetic group, and that is 3c2a1b subclade 2a.2.

With regard to the VE estimate, just to draw attention to a couple of things in this chart, one is that we do not have enough data with which to make estimates for H1N1 or B, so the estimates here are for all Influenza A and for Influenza A(H3N2). There also really is not sufficient data to be able to make any sort of assessment with regard to specific age groups

or specific vaccine types. This is early, and we'll be continuing to follow this and doing those things as is possible if there's sufficient data to do that.

But overall in this table, you can see the adjusted and unadjusted VE estimates from these data thus far for the season. For Influenza A, ages six months and older -- the full study population -- the adjusted VE estimate is 8 percent with a 95 percent confidence interval with minus 31 to 36 percent. And for A(H3N2), 14 percent with a confidence interval of minus 28 to 43 percent.

Now, I mentioned at the top that there's some important limitations here. And one just general one that's always the case with the preliminary estimates is that they are preliminary, and the amount of influenza activity in any given season, even in the absence of the pandemic, is somewhat variable by the time we get to this point in the year. So, these things will continue to be updated as more data become available, and more analysis will be done as more data are available.

Another important limitation to point out here is the low numbers of influenza-positive specimens for this season. The numbers here, five percent positive, represent the lowest influenza positivity observed over the past ten seasons among U.S. Flu VE Network participants with respiratory illness, and this, of course, consequently affects the power to be able to calculate VE reliably and precisely. We have fairly wide confidence intervals also as you see.

Next, the number, again, of influenza-positive participants were insufficient to estimate age-group specific VE or to compare VE estimates for different vaccine products against the predominant H3N2 virus. Again, also, overall, not sufficient to estimate group-specific VE for different ages as is typically done with the data from this network. We still have ongoing circulation of COVID-19. Healthcare-seeking behavior and testing patterns have likely changed during the COVID-19 pandemic in ways that might affect our ability to calculate VE estimates based on the data that are received.

Finally, an additional comment is that the VE estimates here are limited to mild illness. These are people that present as outpatients. Evaluation of VE against influenza hospitalizations is ongoing through another network, CDC's HAIVEN Network.

And, lastly, just a final acknowledgment to not only the staff of the Flu VE Network and their personnel who collaborate with us but also the U.S. Flu VE Network staff at CDC, my colleagues. Thank you very much.

Q AND A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Groshskopf.)It is time for Committee members to ask questions. And I will begin by asking a question regarding the outbreak on the campus. Was it one campus or more than one? I didn't get that.

DR. LISA GROSHSKOPF: The particular data from there is from one campus, and there's a good summary in MMWR that was published, I believe, in late November.

DR. HANA EL SAHLY: No hospitalizations, the outpatient group?

DR. LISA GROSHSKOPF: Overall, I'm not certain, but I don't know for sure that there weren't any hospitalizations. However, according to the data in the MMWR, overall, these were mild illnesses.

DR. HANA EL SAHLY: Thank you. Questions from Dr. Offit. Dr. Offit.

DR. PAUL OFFIT: Yes. First of all, thank you, Lisa, for that talk. Frankly, this is a mucosal virus-like SARS-CoV-2 virus, so you wouldn't expect necessarily that the vaccine would be great at protecting against mild illness. However, you would like it to be very good at protecting against hospitalization and ICU admission. When we present data like this, sometimes this is picked up by the public, and we've gone through this now with SARS-CoV-2 and the COVID vaccines as the vaccine doesn't work.

And so it would be really important, I think, to get data out there on what is protection against hospitalization and ICU admission, which is the goal of

this vaccine. Can you give me an idea of when you would imagine you would have those data?

DR. LISA GROSHSKOPF: The work with the HAIVEN Network -- that's actually adults only and not children, so, there's that limitation -- is ongoing, and I don't think they have enough data yet to present any kind of estimate. But we will stay on that. I can also check back with them and see if there's anything that they're ready to report yet. But to my knowledge, I don't think they've seen enough to be able to report anything.

DR. PAUL OFFIT: Thank you.

DR. LISA GROSHSKOPF: We do have more flu, but it is still low.

DR. HANA EL SAHLY: To follow-up to this, we did not see an uptick in childhood mortality like we would other seasons as well, right?

DR. LISA GROSHSKOPF: No. Fortunately. I mean, unfortunately, we do have six reported, but fortunately, it's not more than that I guess. Is that best way to characterize it? We do have an uptick in

activity, and we only saw one reported last season. So, any one is obviously horrible, but we're not seeing a big uptick, at least not currently.

It's important to keep in mind, though, that the season's not over yet, and we are starting to see in some of the surveillance indices you could see a little bit of an increase, again, for example, in the percentage of specimens that tested positive and some of the hospitalization indices. So, we'll need to keep an eye on that.

DR. HANA EL SAHLY: I meant it as a gauge of severity that Paul was alluding to.

DR. LISA GROSHSKOPF: Yeah, true.

DR. HANA EL SAHLY: Dr. Janes.

DR. HOLLY JANES: Thank you, Lisa. I was interested in hearing you elaborate on your comment about the healthcare-seeking behavior having been influenced by the ongoing pandemic and the implication that might have or the influence that might have on these interim VE estimates. Can you elaborate on what potential effects that might have? Would you expect

that to be differential among the flu positive cases versus flu negative, or would it just essentially affect the denominator for these analyses? If you could comment on that. Thank you.

DR. LISA GROSHSKOPF: I don't know if we have enough information to know whether it would be differential or not, but it's possible that people, if they feel that -- it's possible for, I think, that clinicians might not specifically look for flu, and if they're not using multiple viral test, we might not have that information. It's also possible that people might not be going out to test for flu if they're ill, for example, and staying at home. I don't think we really have a full grasp on how pandemic might've affected those things but those are some of the things that have been raised.

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

DR. ADAM BERGER: Hi. Thanks, Lisa. That was a great presentation and really appreciate all the data and hard work you've done to collect all of this information for us.

I'm going to ask a question that you may not actually have the answer to yet because I noted the whole (inaudible) that you detected are all the H3N2 so far. So, I'm wondering about H1N1 from last season and specifically noticed some of the data that was coming out from the WHO work was indicating that the 5a.1 subclade was poorly recognized by antisera. So, could you comment on how prevalent that was last season as a potential expectation from where we see this coming season?

DR. LISA GROSHSKOPF: That's a good question. It might be better addressed by Dr. Wentworth, I think. So, I think I might defer that to him.

DR. DAVID WENTWORTH: Sure, sure. Yeah. H1 -- - and I'll cover it in my presentation a bit later -- was very low circulation even globally and very low in the United States so far this season. And so that's really where we are with H1. There were parts of central and western Africa where H1 circulated quite a bit, and some parts of Europe, like France, had pretty high levels of H1. And so, there's a mixed bag, and

I'll discuss that between the 5a.1 and 5a.2.

DR. ADAM BERGER: Thank you.

DR. HANA EL SAHLY: Thank you both. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Groshskopf, for your presentation. My question is about co-infections of any of the influenza viruses with either SARS-CoV-2 or any other respiratory viruses. Do we have any data on that?

DR. LISA GROSHSKOPF: We don't have a specific surveillance system that tracks that. There certainly have been co-infections reported in the literature, but we don't have any surveillance specific for that particular attribute, no.

DR. ARCHANA CHATTERJEE: Are there any plans to develop that particularly as SARS-CoV-2 is predicted to become endemic in the future. Are there any plans to track that?

DR. LISA GROSHSKOPF: I can't speak to specific plans at this point, but I can try to get some clarity on that and come back.

DR. ARCHANA CHATTERJEE: Thank you.

DR. HANA EL SAHLY: I see no additional questions to Dr. Groshskopf. Dr. Groshskopf, thank you for your presentation.

DR. LISA GROSHSKOPF: Thank you.

GLOBAL INFLUENZA VIRUS SURVEILLANCE AND CHARACTERIZATION

DR. HANA EL SAHLY: Next is Dr. David Wentworth, director of the WHO Collaborating Center for Surveillance Epidemiology and Control of Influenza. He is also the chief of Virology Surveillance and Diagnosis Branch at the E-Influenza Division. He will take us through a worldwide tour of global influenza surveillance and characterization. Dr. Wentworth.

DR. DAVID WENTWORTH: Thanks very much. And just by way for everybody's knowledge, I have this picture up all the time and I never mention it. This is a picture of an influenza particle. In the light -- oops, we moved ahead already. The light blue parts

were the hemagglutinin which we'll spend a lot of time talking about. And the dark blue, this is the neuraminidase. You'll see that thing with four versus -- there's many more hemagglutinins on the surface of a particle. So, we'll spend a lot of time talking about that. Let's go to the next slide.

Oh, I'm in charge, sorry. So, yeah, this is showing here the WHO-VCM recommendations for the Northern Hemisphere and the meeting that took place last week, and this is benefitted by continuous surveillance that's conducted by the Global Influenza Surveillance and Response System which consists of more than 150 laboratories; national influenza centers, which is what NICs stand for; and led in part by WHO Collaborating Centers, such as your CDC Collaborating Center; WHO essential regulatory laboratories, or ERLs, such as the FDA; WHO H5 reference laboratories. So we also cover zoonotic influenza viruses as part of these meeting and make pre-pandemic vaccine choices for those for stockpiling and readiness.

So, the meeting was held from February 21 to

24. It was a hybrid of an in-person and virtual meeting. It was chaired by Dr. John McCauley. Mike, do you think you can give me that pointer? Thank you very much. So, Dr. McCauley is here. Oops, it disappeared. Oh, there it is. I'm going to need that to work later, Mike. And then had ten advisors --

MR. MICHAEL KAWCZYNSKI: So, sir, all you have to do is click and drag it anywhere on the screen you want or do with your mouse.

DR. DAVID WENTWORTH: Yeah. Hmm. It doesn't seem to be doing it. Now it's moving just sporadically.

MR. MICHAEL KAWCZYNSKI: I moved it for you. I just wanted you to -- we'll turn it off for right now. Okay, go ahead.

DR. DAVID WENTWORTH: Yeah, yeah. Turn it off because it's not working. So, there's ten advisors and eight advisors have seasonal influenza and two focus on zoonotic, and they do this as part of their capacity as representatives for their WHO CC or ERL. I'm going to move to the next slide here; we'll get moving.

I'm going to move pretty quickly through the global activity. We had a nice presentation by Dr. Groshskopf of the U.S. activity. This slide, I think, is nice because it shows you what normal influenza activity looks like in January of 2020 although it sharply fell as SARS coronavirus rose.

But then in July 2020, when we see in the Southern Hemisphere some activity, we didn't see any. Then in January 2021, we had very low activity in the Northern Hemisphere. And then in July of 2021, we also had very low influenza activity. And we started to see a more normal course of activity at the end of 2021 and the beginning of 2022 as you can see here. And most of this was H3N2 globally but with some H1N1 and very little B/Victoria lineage activity, which you can see there. Move to the next -- sorry.

This is looking now at the same thing but over many, many years, and it's just to give you an appreciation for what it normally looks like. And then we had that basically big sieve during the COVID pandemic initiation, the first parts of the COVID

pandemic where we had very little flu activity.

This slide illustrates the percentage of influenza viruses by subtypes and lineage, and so what you can see is that the A viruses dominated for the most part. They represent three-quarters; they're the light blue and the dark blue colors. And the B-viruses are in the orange.

And the numbers aren't really that critical. But the B viruses -- really all of them -- were B/Victoria lineage, and with the A viruses, again, the vast majority were H3N2 with a minority of H1N1. That big section of the pie is unsubtyped, but the proportions would be about the same as what is subtyped.

This slide shows the influenza activity globally, and so as I mentioned earlier, we still had a relatively mild influenza activity all over the globe. Some of the exceptions are parts of Africa, like I mentioned western Africa, where we saw more H1s for example. And then more towards the south and east, we saw more H3 and B viruses. And then China had really

predominantly only Influenza B.

This slide just illustrates the countries and locations/regions where viruses were shared with the WHO Collaborating Centers in this reporting period, so you're getting a sense of where the viruses are coming from for analysis.

And now I'm turning your attention to the H1N1 pdm09 viruses. This is showing the number of pdm09 viruses detected by GISRS over a four-year window from 2019 to 2022. And so, if you look at more normal distribution, such as in 2019, you saw this big peak early in the year, Weeks 2 through 8 about. And then it tails off and then increases again as the following winter begins around Week 2 and 3.

In the more recent times, you can see 2021 and 2022 just really very flatline across that entire spectrum, so very low levels of circulation globally. And this is not due to lack of testing. There's a lot of testing going on for influenza viruses. While it fell off very early in the pandemic, it's continued and done a good job in the number of tests that are

performed.

Now, this shows the influenza activity globally and where we saw some more activity and, as I mentioned, some parts of western Africa. This included some of the coasts like Togo and Ghana, as well as Mauritania you can see had a very high level of activity, and parts of South Africa as well, for example, the country South Africa. We move to the next slide here.

Now I'm going to get into some detail about the H1N1 phylogeny and the phylogeography. And so, by that, I mean, where are these specific clades of HAs circulating? And so, I think many of you now -- I show this very high-level, 50,000-foot level view of the HA gene, the tree, kind of in the middle here between the world and the bars with the tick marks in it. And so that's showing you color-coding by region. North America blue, for example. And so, you can see now, if you go up to where it says 2020 and those first couple of columns, those first months of the year -- those represent months of the year -- you can see all the

dashes and the coloring of those dashes indicate where those viruses were found, and they're associated directly across with certain clades and subclades within that phylogeny, that phylogenetic tree.

And so, this is showing over the course of many years what happened. And you can also see that in the spring of 2020 -- once you get past those first couple of columns -- influenza viruses weren't detected anymore for characterization, and they really didn't pick up again until you started to get into 2021, and the first places you see them is in Africa. So that's towards the bottom of the tree, and they're in the orange. And they represent that 5a.1 group, which the whole group is shown by that big black bar on the far right-hand side, and you can match that up with that portion of the tree. All those viruses are 5a.1 viruses. And that's like the Hawaii/70, which was the vaccine virus.

And so, you can see that some of those made it through the COVID bottleneck and continue to circulate up until the time of this meeting. So we saw more

virus circulation and spreading from Africa now into Europe. So, you can see those green dashes showing up.

Now, if we look towards the top of that tree, you can see this very long branch lines with a batch of small little leaves in that branch. They are 5a.2 viruses. So, these are new derivative 5a.2 viruses related to that Wisconsin/588 vaccine that Dr. Weir mentioned. And you can see all the red there, and these are primarily circulating actually in India with that red meaning Asia or southeast Asia or south Asia. And then a few of them being detected most recently in Europe as well with the green dashes.

And so, what we really saw come through the COVID bottleneck is the bullets indicator: 5a.1 viruses primarily in west Africa and Europe and 5a.2 HA virus from Asia, the Mid-East, and Europe.

Now we're going to get a little closer. I think I'm going to try that pointer again, Mike. See if it works. Um, for some reason it's not following.

MR. MICHAEL KAWCZYNSKI: Click on the pointer, sir, and then just click on the pointer and just drag

it around.

DR. DAVID WENTWORTH: Yep, it's not wanting to do it. Why don't we go ahead -- can you go to the full screen?

MR. MICHAEL KAWCZYNSKI: You know what, sir, I apologize. I apologize, sir. Hold on one second. All right, we'll turn it off right now, and I'm going to go full screen, okay? Whenever you want, all right, sir.

DR. DAVID WENTWORTH: Yes, please. I'll just use verbal descriptions and hopefully people will be able to follow. So now this is a close-up view of a phylogenetic tree of more recent viruses, and so here we're looking at the phylogeography of the most more recent period as you can see really just in 2021 and from September through January so this kind of reporting period. And, again, what we can see is that there's big divisions that are demarcated in the phylogenetic tree, if we go from the bottom now to the top of the tree.

So unfortunately, it's a very different than the 50,000-foot view which went from the top to the

bottom. But as you go from the bottom of the tree, you can see where I've marked that D187. That's the branch point where the 5a.1s formed this group that are like the Hawaii/70 virus, and I've made an arrow there showing you where that Northern Hemisphere 2020/2021 cell prototype A/Hawaii/70/2019 was. And that shows -- that's a representative of the very first 5a.1 viruses. They often share this D187A. If you really look at the small print that's in black, also a Q189E.

Those have continued to circulate and diversify, and as I mentioned primarily in western Africa which you can see the tips that are orange and in Europe which is the tips are green. And so more recently, you see those green tips in say, for example, starting in November and moving into October and January.

Then if you go up the tree a little bit, you'll see where I -- and, oh, I should've mentioned back down in the 5a.1s, you see where I wrote that P137F? That's a new subgroup that's evolved. They have this 137 change and the 155E change. Oh, my

pointers -- oh, the pointers there. Thank you. It must be Mike directing the pointer. And then where the split for the 5a.2s, which is demarcated by that red bar -- those are all 5a.2 viruses there -- is where that 156K is labeled. And there's a number of substitutions in addition to that that make up that group. And we've had further evolution of those in a virus. So that reference virus of that Wisconsin/588/2019, which is the Northern Hemisphere 2021/2022 cell prototype and the recommendation for the '22/'23 season.

There has been further evolution where I've marked that 186T, that big branch point there. And that's where you can see this India/Pune virus from NIV. It's got a very long number I'm not going to read to you from 2021. And that's going to be included in some of these serology studies. So, these dark-labeled viruses are included in our serology studies with post-vaccination sera to see how well those new viruses are inhibited by the post-vaccination sera.

I think these bullets basically say what I

told you and I, in part, put them in there so that those with visual impairments. So, it makes your slide a little smaller, but they understand what the key points are.

Now this shows you antigenic cartography, and it's just taking that HI data from tables. There are many, many tables, and I no longer show them to these kinds of audiences because it's difficult to look at all those numbers. But it puts them in a cartographic map where you can see how related the two virus sets are with each other. And so, the viruses from the HA group are all in the 6B.1A subclades 5a.1, which had that 187, and 5a.2 which had the 156K.

And I did neglect to point out that we've seen a few 5a.1 viruses -- well, I did point them out -- they were the ones with the 137 change, and they also had this G155E which is in a very important position. So, you'll notice 156 has changed in one group of virus and 155 in another. So, this is an important epitope that are targeted by our antibodies and antibodies of animal models.

And the clear thing that I want to have you see from here is the clear antigenic distinction between these two groups. Where it says -- you can see the red dot about in the middle of this cartography -- that says HI/70/19. That stands for Hawaii/70 cell-based antigen. And the egg-based version of that vaccine is the green egg-shaped antigen. And so, you can see how closely related they are antigenically. And they are covering all those blue dots, which are the most recent viruses that have the 156N. And you can see that the yellow dots are a little bit away forming their own little cluster, and those are the ones with the 155 and 137 substitutions.

Now, if you move up towards the top of this map, you'll see the 5a.2 viruses and how the Wisconsin/588 cell antigen really sits right over the top of all the circulating viruses that have been detected recently. So, these include viruses like the ones that I pointed out from India. And then the Victoria/2570 egg vaccine virus showing you there where that antigen sits in relation.

And so, one square in this map is approximately a two-fold difference in the HI titer, and two-fold is the error of the assay. So, two-fold is very little, if at anything. And it's when you get to about eight-fold difference that you can be confident that things are antigenically distinct. Okay, that was a long-winded thing, but we're going to see cartography again, and I won't explain it so heavily.

So, the take-homes from this are we have two antigenic groups: the 5a.1 which are the 187-like viruses and the 5a.2. We have seen some evolution with the 5a.1 that are forming a little bit of an antigenically distinct cluster, but they are still related to the old 5a.1 viruses. The grey dots, I should've mentioned, represent older virus that have been circulated in the past. And you can see how many H1N1s we've had previously. And so, we just had very few circ viruses for analysis because there's very few circulating right now.

Now, this is what is really quite important

now, especially when we start thinking about the vaccine, is the post-vaccination sera analysis of H1N1 pdm09 viruses. And so, I think we'll just keep it on the bigger line because these are very small print. But what we have is we have representative viruses from the 5a.2 group; those are boxed in blue. And they're going to be going down in the column. So we have the Wisconsin/588 vaccine virus or the Victoria/2570 vaccine virus for the cell and egg-based respectively. And then we have this example of the India/Pune NIV 323546 virus which has these additional substitutions like the 186T, but it also has 189V and 224E.

And what you can see is that we have panels of sera from pediatric populations that range from 6 to 35 months and 3 to 8 years, and then 9 to 17 in rows. And then we have adult populations making up many rows from both the U.S., Japan, and the U.K. And then we have older adults from the U.S. and elderly who are greater than 65. These people are not elderly because I'm really approaching that. So, we've got to change that. So, they're 65 or older.

And so now what you can do is go back up to the pediatric. These are the most easy, they're naïve, and they're vaccinated just with this 5a.2 vaccine from the Northern Hemisphere. What you can see is they mount a pretty good response to the 5a.2 -- so blue is good -- and when you start getting into the orange, that's when there is a significant difference between the vaccine response, the geometric mean titer against the vaccine, and the geometric mean titer against the antigen. And so then when you look at the 5a.1 viruses, you can see that in that pediatric population, that's where it's statistically clear that there's not good reactivity with that group.

However, what you can appreciate as you move down into the older people. Those that are vaccinated with either Flucelvax in the top row in the pediatric three to eight or IIV4, which is an egg-based vaccine, we do see some reductions in the geometric mean titers; so, they are coming up as orange. So, you can also see the numbers in the middle there. Those numbers are what the geometric mean titer is, and so if we go to,

for example, the IIV4, the geometric mean titer against Wisconsin/588 is 331, and that against Hawaii/70 is 171. So, it is reduced in the geometric mean titer, but that's still a pretty good titer. And I'll show you a little more data about that as we go forward here.

So what you can clearly see is that there is some reduction to this new India virus, but they're not extremely significant. They're in the light orange, which means the 90 percent confidence interval is just touching the 50 percent bound. That's what that light orange means. And then if you go to the right under the 5a.1 viruses, the one with the 155 substitution has more reductions than the others where you're seeing a better, what we would call, back boost where you see that in blue even though that that wasn't in the vaccine virus. And that you can appreciate, for example, as you get into the adults, it's very obvious.

All right, so this slide, again, illustrates what I just told you. The main high points, again, to help visually impaired. I'm going to move to the next

one.

This slide I think really starts to address the comment by Dr. Offit and discussing VE, and this is a direct measure of individual responses now. So instead of showing you the statistical responses -- which is a very high bar. So, we set that bar up 50 percent, touching the 50 percent line on purpose because we want to know if the vaccine could be inferior for those viruses. So, it's a non-inferiority statistical analysis. So, we want to know if that could be inferior for viruses as to whether or not it should be changed.

The point I'm making on this slide is what really happens when we immunize folks and what happens with their titer. And so, again, we can start with the 6- to 35-month-old at the top rows here. The little blue circles represent what the titers were prior to vaccination. So, the geometric mean titer prior to vaccination was seven, and about five percent of those people would've had a titer above or equal to 40, which is a correlate of protection.

And then post-vaccination, you can see that the geometric mean titer of this very young age group is 43. We don't get huge responses in pediatric populations. But it moves to 60 percent of those now having titers greater than 40 against that Wisconsin/588. It is an egg-based vaccine in that age group, and so you can see it's even higher against the homologous Victoria/2570 egg antigen. And you get about 60 percent of them that would respond pretty favorably to that new variant, the India/Pune virus with a geometric mean titer of 37.

In contrast, the 5a.1 virus of these children look just like the ferrets, where there's a very large difference that they don't get much cross-reactive boost against those 5a.1 viruses in this very young pediatric population. Now that changes when you move to the older pediatric populations such as the 3 to 8 or 9 to 17. Let's focus on the Flucelvax in the 9 to 17 group that's about the second batch up from the bottom. You can see prior to vaccination with the 5a.2 virus that they had a geometric mean titer of 28, and

only about 50 percent of them had a titer greater than 40.

And at post-vaccination, they had a geometric mean titer of 502 -- quite a great boost. And a hundred percent of them now had a titer greater than 40, which is a correlate of protection. So not only that -- so that's the homologous virus -- but if you go over to the column with the India/Pune virus, there was a 437 geometric mean titer, and 95 percent of them have a titer greater than 40. And even more important, if you go to the 5a.1 viruses, which circulated previously, you can see that they get a good back boost to Hawaii/70 with a geometric mean titer that's even higher than the prime they received from the Wisconsin/588. And that's why we call it a back boost.

And so that would help neutralize any viruses that are circulating in the basic 5.1a [sic] group. And then if we look at the 155 column, you also see what we call a forward boost into protecting against those. So, these are the newer viruses that are circulating where you get a boost to that newer virus

with this 588 5a.2 vaccine. And so, it's very out of the genetic group. It has very different characteristics in general, but there's so much conservation that you get a forward boost. And the same thing happens with Togo/881.

Okay, so because this is a public meeting, I am trying to present -- we often present the data that says why the vaccine is bad, what the VE is, what these things are. But really, what this is showing is there's very little downside to being vaccinated. And the other big point is in the very young pediatric population if, in the fall, we have a lot of 5a.1 viruses, we will be messaging to clinicians that they need to be watching out for flu positivity and treating with antivirals because we can anticipate that a vaccine with a 5a.2 will not protect well against those 5a.1 viruses. But that's the only group that that's true in. All these other groups, we have a strong forward boost and back boost.

And so, I won't belabor this, but this is the next slide showing you that the adults, they're in

better shape because, as adults, we've seen many H1N1 viruses in our lifetimes. And you can see, again, that there's -- going to the very first column here -- how good of a forward and back boost we get across these new viruses.

So, to summarize the H1N1 story, we saw viruses that were detected in Africa and Europe and the Middle East, Southern Asia, Oceana, and sporadically in a few other regions. The vast majority of the HA gene sequences belong to the 6B1.A5a subclades. I'm sorry for the alphabet soup. But I'm always going to break it down to the most recent subclades of importance such as the 5a.1, which has this D187A I showed you on the phylogenetic tree. And then we've seen very few viruses that are showing some antigenic evolution that has substitutions at the 137 and 155 that we have our eye on.

And then the 5a.2 viruses, which are the base have that 156K and these other substitutions that I've listed there, they were predominant in the Middle East, southern Asia, and Oceana. And many of the recent

viruses have this 186T along with all those other changes and were represented by that India/Pune virus.

And then the ferret antisera clearly show that the HA clades 5a.1 are distinct from HA clade 5a.2 viruses. So, it's a real dichotomy, and we see both of them co-circulating. It's just not unusual in flu to see two evolutionary tracks happening simultaneously. And these are really trying to evade the host immune system at different parts of the molecule. So, it makes picking a vaccine more challenging.

What helps in picking that vaccine is this post vaccination of sera that was collected from humans. And we have the advantage of this particular selection, which we didn't have in the last selection, was that now we have people that were vaccinated with 5a.2 antigens. And what that clearly shows is that the geometric mean titers against viruses representing the 5a.2s are recognized well for the most part as were of those of the 5a.1, so, the vaccine-induced antibodies that cross-reacted 5a.1. And this is likely because of D-cell memory responses since 5a.1s have circulated

previously and were a component of the 2020/'21 vaccine. The exception were the 6- to 35-month-old serum panels. I showed you that in two ways, both with statistical analysis and just direct representation of the data. And these only react with the 5a.2 viruses, and they are very similar to the data that you get from naïve ferrets.

So, none of the viruses -- I didn't show you the data, but this is always done so that people are aware. We do look for the evidence of reduced inhibition by drugs against influenza, both neuraminidase inhibitors and the endonuclease inhibitors. And so, the neuraminidase inhibitors, none of them showed reduced susceptibility, and the same was true for the endonuclease inhibitors. That's the polymerase inhibitor. So, one inhibits that neuraminidase molecule, and the other inhibits the viral RNA-dependent RNA polymerase.

So, to move on to the H3N2 viruses, these were always the most complex, evolving viruses, the fastest evolving viruses. And typically, you have the lowest

VE and there's a variety of reasons for that and we can discuss those maybe at the end. But the number of H3N2 viruses detected by GISRS is shown on this slide.

I'm just going to focus you on 2021, which is the yellow bar going from Weeks 1 all the way to Weeks 52. And you can see how it increased almost in the normal pattern this time around. Beginning around Week 43, you can start to see that increase. And you can start to see it fall with the red line coming into Week 4 where the data from this particular analysis ends.

This slide illustrates where in the world the activity was happening, and you can see a lot of activity in various parts of the world. The U.S. didn't have a huge season. We had a very small season for the most part, not a strong amount of influenza ranging generally from a zero to five percent level. But in other parts of the world, again, in Europe and parts of Africa as well as Russia had a pretty intense flu season and other parts of Asia.

I also just want to point out here that you can see in South America, for example, Brazil has an

out-of-season flu season. And so, they actually had a flu season that began either very late in their season or very early in their next season. I don't know how you want to describe it, but it's an interseasonal epidemic. But it's caused by these 2a.2 viruses, which I'll point out here.

So now, again, we're looking at that black phylogenetic tree kind of in the dead center of this slide and then the color-coding showing you where the tick marks are. And we can look at this, the evolution of the virus since 2020 through 2021 and the beginning of 2022, basically. And you can see that in the beginning, the viruses were either 3a viruses, and they were found in Europe. It was in the early parts of 2020, and those green tick marks as you come down that tree. And then we have the 2a viruses, and they split into the 2a1b.1, 2a1b.2 groups. And then, now you can also see what's come through the COVID bottleneck. And you can see it in Africa. We had 2a1b.1a viruses and 2a1b.1b viruses that still continue to circulate and some of those spreading to Europe and a few other

regions.

Then, if you come down towards that major part at the bottom of the tree, it includes the 2a1b.2, which is that long black bar. That breaks up into the 2a1b.2b viruses and the 2a1b.2a viruses. And so, the 2a viruses are the more recent viruses. And the first ones to come through the bottleneck were 2a.1 viruses, and then the second group were the 2a.2 viruses. So, the .2a2 and the .2a1.

And so, you can see how those 2a.1 viruses were primarily in Asia and then started spreading to the Middle East and Europe. And that was -- that's what's showing you here in the bullets. And then the 2a.2 viruses were in Europe, Russia, North and South America, and it increased from 2021 to 2022. I'm going to move you to the next slide.

This is just showing you a more simple blow-up of all those clades, and that's what's called a time tree. So, time is at the bottom rather than genetic distance, which is usually what's the x-axis. And what you can see here, what you can easily appreciate, is

about the top half of that tree where you see -- we'll just start at the very top with the dark blueish purple dots. Those are 2a.2 viruses that also have additional substitutions, one including this 53G which it's marked at.

And that X represents the vaccine virus Darwin/6, and so that shows you where it sits in the viral evolution. We've also seen the next batch down, the 2a.2s with 53N, they are the light green dots. And 2a.2s that are just more of the standard original 2a.2s; you can see they circulated earlier in 2021 and really gave rise to these other viruses. And they're in the goldish-yellow colors. So, then you can see the next X and that's the Cambodia vaccine virus, and those viruses that are the blue dots that are the 2a1. So 3C.2a1b.2a1 viruses that are circulating.

And what you can also appreciate about this graph is that a small proportion of 1a viruses -- which are near the bottom there, they're the yellow dots -- and the 1b -- which are the darker green clades -- are still circulating. And so, these are closer related to

the older vaccine virus but have made additional substitutions. So, the main point I want you to take away from this is that the 2a.2 viruses now predominate.

There's a large cluster of viruses and they continue to diversify. I would also like you to know, you can see where that X is? That shows the month of the year where that virus is isolated, and you can see that this virus, Darwin/6, which represents the 2a.2 viruses was isolated about a month after the vaccine consultation meeting and a few, two or three, weeks after we met for the VRBPAC. Just to give you a sense of how fast flu evolves.

This slide shows the geographic distribution of all these clades. I don't think we have to get too involved here. I'm probably speaking a little slow. The HA clade 2a.2 predominant globally. The predominance of the subclades differ regionally, and I tried to point that out on a few other slides; but here I can point it out easier, I think. If you look at the D53G viruses with the 156S and 157I, those are the

purple kind of color, you can see they really predominate in North America. That was basically what happened in that outbreak that Dr. Groshskopf discussed in the VE presentation.

These were all these viruses with D53G in addition to the Darwin/6. They have the D53G and the 157I. Darwin/6 is a very advanced virus that does contain the 156S substitution, which is common in most of the viruses circulating now. Then you can also see the D53N group; that's the lighter green with 96N, 156S, and I192F. And they are from western Europe such as the Netherlands and Sweden and in the South America and Brazil.

The clade 1a viruses are circulating in Africa, Côte d'Ivoire, Ghana, so, in Western Africa, up in Nigeria, but also in Ethiopia more towards the east there. So then, we have those viruses circulating there, and the clade 1b viruses were only sporadically identified in those countries listed. I won't walk you through that.

So now, where are these substitutions that

this genetic difference is in code? What I'm showing you here is on the left the Cambodia/E0826360. This is the Northern Hemisphere 2021/'22 vaccine prototype -- so, you can still get this vaccine. There may still be time; we could have a late flu season -- and the Southern Hemisphere 2022 prototype, the Darwin/6 which is also the recommendation for our Northern Hemisphere 2022/'23 season.

The one thing that you should be able to appreciate is that they share a lot of the same substitutions. So, all of those red dots that you see on the molecule represent changes from the prior vaccine A/Hong Kong/45/2019. And many of these are very important antigenic sites. Sites A and B at the tip or head of the molecule, those are the kind of light colored -- the kind of light tan color and the light green color. So that's showing you the epitopes. And then the light yellow is a different epitope and blue is a different epitope and the dark blue is a different epitope.

But many of these substitutions such as 137S,

186S, 135T, these are very important epitopes in the molecule, and they're shared between Cambodia and Darwin. The difference between these Darwin-like viruses, which are the 2a.2 versus the 2a.1, are the additional substitutions at 156S. A big one is that one at 159N. And another large change is the T160I, which has that little star symbol next to it. You can see where it is in the 180-degree rotation right at the tip of the molecule.

And that position leads to a removal of a glycan at position 158. So, a glycosylation site at 158, and that's a very important antigenic distinguishing feature of H3 viruses that first emerged in 2014 and has continued since that time. So that represents a change.

So here this shows the summary of the antigenic analysis of the antigens recommended for the Northern Hemisphere 2021, again Cambodia. And you can see now these viruses can now be hemagglutinated again, and that's partly because of that T160I and the 158 change now allows it to bind red blood cells in vitro,

and we can use hemagglutination inhibition assays as a surrogate for virus neutralization. And two of the CCs did that quite a bit: the Francis Crick Institute, which is FCI; and VIDRL. And you can see their total data here with only 18 percent considered like against the cell antigen and 82 percent considered low, so an eight-fold or greater to the homologous titer, and the egg was a little bit worse where you had only six percent considered like.

Going down to the neutralization assays, you can see the totals here where about 18 percent are considered low. So very consistent with the HI assays -- I mean, 18 percent considered like and 82 percent considered low.

Now moving into the Darwin/6 cell analysis. It's really the opposite where 85 percent are considered like in the HI assay in the antisera against the cell antigen. And the antisera to the egg antigen, 64 percent are considered like. Not too bad for an egg antigen. And by virus neutralization, it's actually a little bit better.

This shows you the antigenic cartography. Again, the 2a.2 viruses are antigenically distinct from the 2a.1 viruses and the 1b viruses. And so, this is a little bit high-level view where the 2a.2 viruses are the brown and green dots up in the top. So the key is right here. I'm sorry there's so many colors, but we were really trying to determine if the 156S versus the 156S with 53G -- which is the lighter brown color -- and the 156S with the 53N -- which is the olive-green color -- were antigenically distinguishable.

And what you can see is that they all kind of intermix in this antigenic map indicating that there is not strong antigenically distinguishing features by the addition or subtraction of these amino acid groups. And then with the Cambodia is this kind of orange circle down near the bottom. You can't see the label very well, but it says CA/20 cell. That's the large orange circle, so it shows you where the Cambodia is; and the bright fuchsia circle shows you where the previous vaccine Hong Kong/45 is. So, you can see that they're antigenically distinguishable from the Darwin-

like viruses or the 2a.2 viruses.

And those bright green ones off to the left where it shows KS17, that's the Kansas antigen from 2017, and you can see where that sits. And so, there's been some convergent evolution between that group of viruses and the most recent viruses. And you may remember that's the virus that we had to delay the vaccine decision for to make that vaccine candidate.

So, this shows you a closer view of both data from using HINT, which is High-contrast Imaging Neutralization Test. It's a new technique we developed at the CDC that can really distinguish small antigenic features and a closer view of the work from the HI data in Crick at the London CC.

And so, you can see how the data really looks quite similar between the two groups and that we don't see the same huge distinguishing features between the various flavors of the 2a.2 subclade viruses.

Now here's looking at the human post-vaccination serum. Multiple serum panels do show reduced reactivity. Remember, they were vaccinated

with a 2a.1 virus against the 2a.2 viruses, so they are statistically -- we can see in the dark orange colors as you get in that orange bar down there. That's where we have significant statistical difference where they would be considered inferior. The vaccine antigen may be considered inferior against those particular antigens.

So, you can see a stark contrast here, but what you'll also see, which is probably important to note is that the newer 1a virus like the Togo/771 is well protected. So, people that would be potentially infected by that virus would be better protected with the current vaccine, and the 1b viruses we're still getting great cross reactivity, so back boosting against those.

This slide now goes back through those bubble plots, and I just want to focus you on the 2a.2. So, we selected last year a 2a.1 virus, which were really the viruses that we had available and were the new emerging group. And you can see, again, in the children, it doesn't work so great in the very young 6

to 35 months old, very similar to what we saw with the H1.

We'll now just go to the second set of rows. The Flucelvax set of columns; you can see a forward boost. So, you can see both a back boost -- so Cambodia you can compare that SIAT column, so that's the cell-based Cambodia. It has a geometric mean titer of 171 post-vaccination. So that improved to a geometric mean titer of 30.

And, if you look across that column, you can see that against the total 771, which is a different variant, it has a geometric mean titer of 166 -- so not bad -- and 75 percent of them now are above 40. The same is true of Hong Kong/45 where you get a little bit higher titers. So that's what we call our back boost. It's boosting into the older viruses with a higher geometric mean titer than the homologous antigen. So, it's 219 instead of 171. And then as you move into this antigenically advanced group -- clearly advanced based on the ferret data, the Darwin/6-like viruses -- we still have a GMT of 89 and 70 percent considered

above or equal to 40.

Basically, the same numbers for these more advanced viruses such as the Maryland/02 with the 157I and D53G substitutions. And the Alaska/01 representative, which is that other group, the D53N and 186S. So, we try to pick these new emerging groups for analysis in the closed vaccination serologic analysis.

I won't walk you through this slide. I think it's basically the same. We saw with adults, vaccination increased titers to HA clade 1a, 1b, 2a.2. And remember this is a 2a.1 vaccine. So, we saw both back boost and a forward boost against recent 1a, multiple 2a.2 variants, and the titer and forward boost reduced in older adults and elderly.

So, I did want to -- maybe I'll point that out. If you look at the pre and post here as you go down this column into the elderly, you don't get as strong of a forward boost as you see with the adults, both in Flucelvax, and Flublok, and the IIV4.

So, to summarize the H3N2, in many countries, areas and territories reporting Influenza A(H3N2)

subtype predominated. And most countries in Europe, North America, Middle East, South America, and some countries in Africa -- they are listed there -- where we saw H3N2 predominated.

The phylogenetics of the HA show that the H3N2 virus is circulating in this period really belong primarily to a variety of subclades -- the 1a, 1b, 2a.1, and 2a.2 -- with the most recent viruses being this 2a.2 HA clade that's predominated and continued to diversify into two main subgroups that we'll probably be talking about in the future. Hopefully, one of them will die. The D53G subgroup with 156S and 157I; or the D53N subgroup with N96S, which affects another glycosylation site, and N156S and I192F, which is right up in the head of the hemagglutinin molecule.

The antigenic characteristics. All the 2a.2 viruses were antigenically distinct from 2a.1 and 1a, 1b viruses. And this ferret antisera really delineates that. It's here for posterity. We go into the human serology studies; however, post-vaccination GMTs were significant when reduced against those 2a.2 viruses.

And viruses with the HA and the 2a.2 subclade, that were either the 53N or 53G, all showed similar reactivity patterns. So, what I'm saying there is they were difficult to distinguish antigenically at this time.

And nevertheless, the 2a.1 vaccine provided forward boost against 1a and 2a.2 viruses, and often the majority of individuals had titers greater than 40. And so that's a plug for why we get vaccinated even if there's an antigenic quote distinguishing virus that's emerged.

And antiviral susceptibility genetic and/or phenotypic testing showed that only one of a thousand viruses -- more than 1,000 -- 1,023 -- collected after September 2021 showed reduced inhibition to the neuraminidase inhibitors and even better shape in the baloxavir. Out of 962, none showed evidence of reduced susceptibility.

Okay, so now it's time to talk about the Influenza B viruses. This shows you the number of B viruses detected by the GISRS, again, the yellow bar

showing you the 2021 flu season -- or year I should say -- and, again, beginning to see a subtle increase beginning as early as Weeks 35 but just really gradually increasing all the way into Week 52 and then declining from that point in the red bar, as you can see -- red line.

This shows you the Influenza B viruses ascribed to their lineages, the numbers and the percentages where basically -- I'll just give it to you in a nutshell -- virtually all the viruses detected were B/Victoria viruses. And there were some where the lineage was not determined.

This slide shows you the activity. And as I mentioned early on, China didn't have activity in other viruses, but they had a lot of activity in Influenza B, along with Madagascar. And so, a lot of the data for this B decision came out with China National Influenza Center, which is also a WHO Collaborating Center.

Now, we're looking at the high-level phylogeny, 50,000-foot view again, showing you how the B viruses have evolved over the years, and the first

set of big drift variants came as the V1A.1. As you start falling from the top of that tree, you can look to the long black bar about a third of the way down. That was called the double deletion variant that had the deletion of the amino acids 162 and 163 in the hemagglutinin molecule.

And then came the triple deletion variants which is the very long bar going down. You can see now in the very first columns where there's tick marks, you can see the blue and the green and red, small red tick marks. That is the triple deletion viruses. The first virus is circulating there, and that is represented by the Washington/02 virus that was in our vaccine, for example. And they continue to evolve.

So, what's come through the bottleneck of COVID is these 1A.3a.1 and 3a.2 viruses. And so, you can see all those red dashes and a few orange dashes there indicating China, Africa, and very few blue and green in Europe and North America. And so, in China, they had both these 3a.1 viruses, and they had 3a.2 come in later and begin to displace the 3a.1.

This is a close-up view now of the phylogenetic tree, looking closer now at the top of this tree, the 3a.2 viruses. We can see at the very top of this tree all of those red dots that don't have any -- they're vertical, that's called monophyletic. So that means all those viruses are virtually -- their hemagglutinins are virtually identical to each other. It's not even a nucleotide different.

So that's just really an epidemic virus doing very well in the community. And a recommended vaccine prototype is labeled up near the top of that tree, B/Austria/1359417. Both the egg and the cell are nearly identical, and they're both shown on the tree there. So that's the egg prototype and the cell prototype. They do have minor distinguishing characteristics.

That's the main thing I want to focus you on the 3a.2s. And then the 3a.1s are about the mid-level of the tree, and they're represented by that B/Sichuan-Jingyang virus. And that will be in the serology study that I'll show you later, along with as we go up some

new diverse 3a.2 viruses that have this T182A/197E that's boxed like B/Henan-Xigong. I'm sorry, I can't pronounce that correctly.

Oh, I want to point out where Washington/02 is. So, the current Northern Hemisphere cell prototype is this Washington/02. It's down here in the base of the tree. So, all the viruses really are derived from viruses like Washington/02, and they're in the 183 group. And that was our Northern Hemisphere prototype that we got this year.

So, looking at the viruses characterized during the last three reporting periods, you see that there's just been very little B circulation after the 2019/2020 season except in China where you can see the 2021-to-2022-time frame. There was more than 1,600 viruses characterized, so many more than that identified.

Again, this is a high-level view of what the analysis of the antigenic analysis of the viruses looks like. So, this is antisera against either the Washington cell recommendation or the Washington egg

recommendation. And you can see that in the United States, for example, at the CDC, 68 percent were still considered Washington cell-like. But the CNIC, which is the China National Influenza Center, only 38 percent were considered like. And so it's really showing you the geographic differences between what's circulating. And 62 percent were considered low there. Overall, the totals show that only 38 percent are considered like Washington and 62 percent considered low, really illustrating that globally antigenic drift is happening. And then if you look at the egg-based vaccine, it's actually quite similar with 33 percent and 67 percent respectively.

Now, looking at the new recommendation for the Southern Hemisphere 2022 and the WHO recommendation that we are considering today, the B/Austria/1359417 virus, you can see that 88 percent are considered like and only 12 percent are considered low. And, again, you can see some geographic difference there with the CDC seeing a little bit higher percentage considered low to that B/Austria virus antisera. And a very

similar phenomenon with the egg, the egg actually looks one percent better considered like -- so I'd call that the same -- and 11 percent considered low.

Again, showing you the antigenic cartography. Now this is coming from data from the collaborating center in Beijing that produced all this data. And so, again, you can see these various HA subclades. The 3a.2 and 3a.1 viruses are antigenically distinct from the clade 3. And so, if you really look at the green viruses versus the yellow there to see that, how far apart they are and where that Washington/02 cell and egg are shown.

And then, also, where viruses, even in China, that were circulating that were more like Washington. But you can see how they had many more viruses that were the 3a.1 or 3a.2 viruses. And you can see where the B/Austria egg virus sits amongst all of those. It's that big oval-shaped dot.

And so, you can see that the various subgroups are antigenically close related, and they form overlapping clusters. So, all the 3a.2 viruses really

are forming overlapping groups, again, so the different colors of light green there. There's an olive-green color showing you the 3a.2s with the 197 substitution and a very hard to probably distinguish on your computers, but an in-between green color, a little bit darker than the light, light green, is the 122Q.

Again, so we're seeing some genetic diversity that's not equating to antigenic features that we can tell yet. And then in darker green are the 3a.1 viruses that circulated primarily only in China. And you can see they form a distinguished -- a related, but antigenically distinguishable group from the 3a.2 viruses.

Now, looking at the post-vaccination in humans serum analysis. Now, remember in the Northern Hemisphere, people were vaccinated with the Washington/02, which is the older V1A.3 virus. You can see that even in the very young pediatric population, while the titer was low, it was pretty good cross-reactivity even into the 3a.2 group.

Looking at that Austria-like virus, that's the

new vaccine prototype, but we did see some reductions again once you get to that further involved Henan-Xigong virus that had the 122Q, for example, or the Maryland/01 virus that had that one 127T and 197E that I pointed out on the tree. But then when you get into the older populations, you can see great cross-reactivity across these two different clades or forward boosting would be another way to put it. I'm not going to bother showing you the bubble plots for that. The statistical analysis shows it.

If we go to the B/Yamagata lineage viruses. These are the unseen viruses so far. So, B/Yamagata lineage virus detections have really been very sporadic and occasional reported to the FluNet system within WHO and only 13 positives reported. But none of those had been confirmed by WHO Collaborating Centers. So, we request these and try to grow them or retest, and we have not confirmed any of those viruses yet. And no viruses of this lineage -- B/Yamagata -- have been available for analysis during this period, so that will save us some time. I won't show you data from them.

No B/Yamagata/16 viruses were detected or confirmed so this is for future considerations since March 2020. And it's unclear at this point if this lineage are truly extinct and hence, for the 2022/'23 Northern Hemisphere quadrivalent influenza vaccines, a B/Yamagata lineage virus is still recommended. The recommendation hasn't changed from the B/Phuket virus.

The WHO GISRS in consultation with other parties will reconsider the situation in about a year as to the necessity for including B/Yamagata lineage viruses in influenza vaccines.

Only B/Victoria lineage viruses were detected, so as part of our summary for Influenza B here, the HA phylogenetics of the B/Victoria lineage viruses, nearly all the HA genes belonged to subclade 1a.3 that has deletion of residues 162 through 164 and an additional K136E substitution. So, everything's really derived from that type of a virus, which B/Washington/02 is a representative of. We've seen further evolution of this HA gene to the 3a, which include these additional substitutions: the 150K, 184E, and 197D. And that's

really what came through the COVID bottleneck were these 3a-like viruses. And they've continued to evolve, and two subgroups have emerged. The 3a.1, which has these additional changes at 220M and 241Q. We did discuss this last VRBPAC meeting. They've just had kind of evolved, these two groups.

And then the 3a.2, which have this 127T, 144L, and 203R, which were seen more globally: Asia, Africa, Oceana, Europe, and North America, although with limited circulation in those places in contrast to China which had heavy circulation of Influenza B. What China was also able to delineate as part of the Southern Hemisphere strain selection was that the 3a.2 virus started to out compete the 3a.1 viruses. And so, it started to displace those in China and have continued to do so. The 3a.2 viruses have further genetic divergence, and they have additional substitutions encoded in viruses from different geographic regions.

However, those were not antigenically distinguishable. And so, I'd like to remind you about

the Yamagata. We haven't really seen any, although 13 were reported and no viruses of this lineage have been available for analysis.

And I'd like to acknowledge all the other WHO Collaborating Centers, the entire GISRS of over 150 laboratories that make this system function, our partners at the University of Cambridge who do their large 50,000-foot phylogenetic trees and the antigenic cartography that I showed you.

The essential regulatory laboratories are key partners in this, like FDA, TGA, NIBSC, the U.S. partners, the Association for Public Health Laboratories. Of course, the United States Air Force School of Airspace Medicine, they are very great partners; we have collaborated with them. In fact, the Maryland/02 that you saw used in our serology assays came from an outbreak in Maryland in a military location, and we were able to obtain that very early before even the college campuses had outbreaks. But thanks very much. The Naval Health Research Center is also a collaborating partner in that group.

The fitness forecasting partners, I showed you very little data from them, but I did show you a tree from Trevor Bedford and Richard Neher Nextstrain site. I think it'd be easier for most people to understand than some of my detailed trees. And then, of course, our influenza division staff. Thank you.

Q AND A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Wentworth. The (audio skip). I would like to invite my fellow Committee members to raise their hand if they have a question or comment on the presentation of Dr. Wentworth. I will begin.

The H3N2 2a.2, how is much of the disease here and elsewhere but when you showed the -- we call them the bubble plot -- I think that most individuals who are vaccinated with the season virus has good HAI titers which are for -- so that led me to the question, did we see maybe more variability in the HA neuraminidase of that particular virus compared to the

(audio skip) or -- because the factors looked good, but I don't know.

DR. DAVID WENTWORTH: Yeah, very, very interesting question and very important question. And because the HA is the primary target of all of our vaccines, although we do a lot of neuraminidase phylogenetic analysis, and some we did antigenic analysis of the neuraminidase this time, I left it out because of time. It's three or four viruses we have to cover in some detail, so I didn't show the neuraminidase data, but we do look at it.

The neuraminidases of the viruses that are circulating are very closely related to the Darwin/9 egg neuraminidase and pretty close to the Darwin/6 egg neuraminidase. So, it's a great point, but we haven't seen a lot of evolution in the neuraminidase that would suggest that's part of the evasion. I mean, it's evolved from the earlier influenza viruses, but there's some pretty important sites that affect a glycosylation that exists in the Cambodia. The older vaccines, all the 2a viruses have that, whether the 2a.1 or 2a.2. So

that we know is an important antigenic characteristic shared by both vaccines. So that's good. And so that doesn't really explain, like the VE data that you saw earlier.

I would point out -- I mean, I would think that that VE data is critical and we have to pay attention to it and it is a self-check on our selections that we make prior to knowing what's going to happen. I think that the serology data is a more direct analysis of what happens when you get vaccinated. And so that's why we've added it to the VRBPAC in more detail over the past couple years in response to the Committees' questions. And I took such a long time going through it today because, in general, people don't realize the good.

If you look at those pre-titers, those blue circles, there's no hope. And if you look at the red circles or orange circles, many people are pushed above 40 which is a correlate of protection. So, there is this dichotomy between what the VE tells you and what the serum tells you, and neither is right. So, there's

some that will be above 40 that wouldn't be protected. Some might be 40 and below and still protected, and so it's a very difficult question.

But with regards to the VE, we didn't have what we call a lot of virologic pressure. Even the little peak of H3 we had this year was small in comparison to previous years. So only getting up to four or five percent positivity rate when some years it's 18 percent. Right, so when that infection course is very low, it challenges a negative test design VE to really produce strong data because you don't have enough infection force. And personally, I read that VE data as the range that's lifted there. It's either minus 24 to 39 or this point estimate of 14. When it crosses the zero, it's really statistically insignificant.

And so, if you looked at it instead of the point estimate as the range, what you really are saying is that we're not super confident in that point estimate. It's crossing the zero, and it's going up. It could've been 43 or whatever the top part of that --

I'd forgotten what Dr. Groshskopf showed -- but also that's preliminary data in part because they haven't gotten all the data in from the people that were infected in a very weak influenza season. Sometimes, if H3 peaks very early and we have a lot of virus around, it's much easier to get a strong point estimate with a narrow confidence interval around VE.

And I do think the U.S. armed forces were able to do that and have a tighter confidence interval that is above the zero and do have a little bit better point estimate. So, I think in the U.S. VE network it went from somewhere from minus 28 to 43, right? So, it could be as good as 43 or as terrible as 0 because there's no such thing as negative VE, right?

Also because this is a public meeting, I want to point that out. That negative number does not mean that the vaccine causes more flu, okay. That negative number is the statistical analysis negative number, and when it crosses the zero, it really makes us nervous about the point estimate -- not nervous, uncertain about the point estimate. We're trying to show you in

that range the uncertainty that we have in the analysis, and Dr. Groshskopf did a great job showing all the things that could affect it, including the unusual COVID pandemic situation where we have health-seeking behavior that is much different than normal. So, probably a lot of caveats on the VE.

DR. HANA EL SAHLY: Probably a lot of the testing in the outpatient also strictly tested for SARS-CoV-2 and not the multiplex.

Thank you, Dr. Wentworth. I do not see any raised hands. So, if we don't have any additional questions or comments, we will take a break.

DR. DAVID WENTWORTH: That either means it was not very clear or it was very clear. I don't know. I hope it was clear. But in the end, we did discuss at the outset alternatives. I don't want to make this seem like it's a fait accompli analysis. There is always the option if the Committee feels very strongly. We won't be able to necessarily answer a question today. I might have to go back. We might just set up another meeting so I could give you some alternative

candidates. But we always are looking at that. And as Dr. Weir mentioned, the U.S. does have fairly strong representation in the WHO committee.

There was one season very long ago where the VRBPAC chose to choose one of the strains differently, for example. And the other thing we've done as a committee for the WHO -- I kind of mentioned it in this talk briefly -- but just for historical reference; nobody felt comfortable with the decision on the H3 virus at the time the decision had to be made. And therefore, the entire WHO committee postponed the decision until we had more data on a very recently emerging H3 virus and were able to successfully get a candidate vaccine virus and distribute it globally with only a month delay.

That did cause some manufacturing delays, and it's important that manufacturers don't take lightly to postponing that. But just for everyone's awareness, if we are uncertain and we have to, we will postpone a decision.

DR. HANA EL SAHLY: Okay. Thank you. I have

now two members with questions, Dr. Janes and Dr. Portnoy. And we will begin with Dr. Janes.

DR. HOLLY JANES: Thank you, Dr. Wentworth. I really appreciated the care and time that you took to go through this today. I wanted to follow up on your discussion of the limitations and interpretability of the preliminary VE estimates versus the immunological and phylogenetic data that you've presented. This Committee is always presented with these preliminary VE estimates, and they're especially limited in quantity and quality this year given the pandemic.

Does any set of this team go back at the end of the year once the final VE estimates are in and correlate what the VE estimates with what was seen based on the immunology and the phylogenetics to help us prioritize and interpret the relative merits of these different data types? I mean, after all, I think we'd all agree that the VE estimates are what we care about. It's just that they're limited in precision, especially this year and in general, always limited in precision when we look at subgroups and vaccine type

and so on.

DR. DAVID WENTWORTH: Yes. Sorry, every time I turn my microphone on my phone talks for a while. So, yes, this is done. So, there's two things that happen. One, a full VE estimate from a season is nearly al- -- if we have a strong enough season -- is nearly always published in a variety of different journals. So that's done. The cohort that we get the vaccine serum from and the VE data are completely separate. So that's a little tricky, but we definitely look at the trends.

Third, when we have a special study such as what Dr. Groshskopf mentioned with the campus outbreak, there they can do a combination, and there's still more and more analysis happening with that outbreak, I think, that we'll be looking if possible, having serum from individuals. Not only were they vaccinated, but how well did they respond to the vaccine? That is one of the challenges of the influenza vaccine. It's very safe, not very reactogenic, and so there are a number of people that just don't mount a strong response once

they are vaccinated. So that does happen.

But usually, when would it -- I guess I would anticipate that young adults in the college-age setting probably would've had an okay response. Clearly, there's -- I think within that paper or in some preliminary data, there isn't strong neutralization titer among those vaccinees against the Darwin/6-like viruses that circulated in that location. I'm not sure why I'm not telling you which college campus it was, but I think it's published. But I don't know if that's okay, so I'm just not going to mention that. But it's just a college campus location. It's a big campus, big college.

So, yes, we do. The long-winded answer was that. But the short answer is, yes, we do try to correlate those things when we can, and that's one of the advantages of doing an EPI8 and working with public health partners that are so great on those studies.

DR. HOLLY JANES: Thank you. I guess just to follow up on that, I wonder if it's worth considering if that would be appropriate to present to us at some

point. It would obviously apply to past years when the final VE estimates were in. But I think it would be informative for interpreting the current year's immunological phylogenetic data.

DR. DAVID WENTWORTH: Thank you.

DR. HANA EL SAHLY: The last question is from Dr. Portnoy.

DR. JAY PORTNOY: Oh, good. I always like to get the last word. No, your presentation was amazingly clear and somewhat overwhelming. I think that may be part of why we aren't getting a lot of questions. But thank you for that presentation, it was really helpful.

My question involves the wisdom of including the B/Yamagata strain in the vaccine. We only have room for four strains, and one of them is a strain that's essentially extinct. My understanding is that the intent is to give it long enough so that it actually becomes extinct. Only one virus in history has actually undergone that, and that's smallpox.

And I just question the need to do that because there were no strains isolated this last year.

Wouldn't it be more prudent to maybe include the A5.1 along with the A5.2 just to get more complete coverage as opposed to using up one of the four available slots for the B/Yamagata? Do you have any thoughts about that?

DR. DAVID WENTWORTH: Yeah, thank you very much for that question. And I think it's an important question. And there's a couple of things going on that I'll try to address. One, there is a large iceberg of influenza. It's a simple way to think about it. B viruses, A viruses, the viruses in animal reservoirs, luckily with B viruses, they primarily only infect humans. So that's one important difference from A viruses. And so, there is potential that it is extinct, and in part, it makes a lot of sense because the first thing that happened if you think about the Influenza B viruses is we had a double deletion variant which swept the world and really stimulated immune responses that likely cross-reacted with the B/Yamagatas.

And then, subsequent to that, we had a triple

deletion B/Victoria variant that also did the same thing. And then, right after that, SARS coronavirus happened where we had all the mitigation associated with preventing the COVID-19 -- you know, mitigating the COVID-19 pandemic. So, all three of those could easily have strongly contributed to the kind of extinguishing of the B/Yamagata lineage.

However, as I mentioned, there's a very large iceberg. Our surveillance is not complete in any one country, let alone the world. And so, there could be small pockets of B/Yamagata still circulating that could emerge, and we want to be cognizant of that and include the B/Yamagata in the vaccine.

And then the second kind of related but unrelated part/answer to that question -- and I can turn it over to the FDA -- is a regulatory question. And so right now the licensed vaccines are quadrivalent, and they have one of each of the components: A(H1N1)pdm09, A(H3N2), B/Victoria, and B/Yamagata. You can't just substitute another H1 or another H3 into that licensed vaccine.

So there needs to be a lot of work done in probably pre-clinical and clinical settings to understand reformulating the vaccine like that and putting two of H -- I think most of us are discussing putting two H3s. H1s induce pretty good cross-reactivity. H3s are a little more challenging, and so it would be really -- to make my life a lot easier if I could pick two H3s. I could tell you that. The whole Committee would be happy.

So that is something that I think a lot of researchers are starting to investigate. While we wait, basically time will tell if that B/Yamagata lineage is truly extinguished. As I said, we had 13 detections. Most of them were very high CT, so in PCR, they were PCR detections. So, they had very small amounts of virus genome in that detection, and they could not be isolated.

And the other confounding piece is in the live attenuated vaccine -- which is quadrivalent -- there is B/Yamagata lineage. And so sometimes, someone may get the live attenuated vaccine, and then, for whatever

reason, they're tested maybe a few days later and they come up positive for Yamagata. So, some of those might be live attenuated detections and some of them might be real but so low we can't isolate a virus.

And so, just picture an iceberg and think about there's a lot under the water that we don't see, and our only real test will be time to know that it's fully extinguished. And then potentially setting up very in-depth studies where you go look specifically, like very deeply, for B viruses and Yamagata lineage viruses.

DR. JAY PORTNOY: Great. Thank you.

DR. DAVID WENTWORTH: A lot of people considering that open window of 15 micrograms of antigen that could be different than a B/Yamagata.

DR. JAY PORTNOY: And I agree with you. I think that the FDA or whoever makes those decisions ought to reconsider reformulating the vaccine to possibly include more or different strains. But thank you very much.

DR. DAVID WENTWORTH: Yeah. I think it would

have to be probably led by the companies, and they would have to petition the FDA, here's our data and this is why we think we can do it. But I can turn it to them.

DR. JAY PORTNOY: Thank you.

DR. HANA EL SAHLY: And, Dr. Weir, is going to probably try to shed light on this question.

DR. JERRY WEIR: Dave, you gave a great regulatory answer. I'm not sure I have to add much. It is true that any changes like that were being discussed would have to be chan- -- the manufacturers would have to change their licenses, and that would require data. Of course, it can be done. But, yes, you would have to -- just like when we added the fourth strain that required data from each individual manufacturer to change their license.

The only thing I do want to add is that all of the manufacturers are still licensed to produce a trivalent. So, if for some reason there was a recommendation coming that said there really is no point in adding a fourth strain, they would not have to

change licenses to go back and produce a trivalent. Their license is still in effect for that. But, yes, data would be needed and it can be done and it could be done. But it would require data and an updating of their license. Thank you.

DR. HANA EL SAHLY: Hmm. All right. Thank you all. I turn the meeting over now to Michael Kawczynski for the break.

MR. MICHAEL KAWCZYNSKI: All right. Thank you. And thank you for all the speakers and I'll say our first morning portion of today's event. Looking at the time, we're going to take a short ten-minute break, so we will reconvene at 11:25.

[BREAK]

DoD INFLUENZA SURVEILLANCE AND MID-SEASON VACCINE EFFECTIVENESS

MR. MICHAEL KAWCZYNSKI: All right, and welcome back to the 171st Vaccines and Related Biological Products Advisory Committee Meeting. This

one's on influenza. I'm going to hand it back over to our chair, Dr. El Sahly, go ahead, take it away.

DR. HANA EL SAHLY: Thank you, Michael, and welcome back. So, next on our agenda, Dr. Courtney Gustin. Dr. Courtney Gustin is from the Armed Forces Health Surveillance Division, Global Emerging Infectious Diseases Surveillance Branch. And, Dr. Courtney will give us an overview of the DoD influenza surveillance and the (audio skip), Dr. Gustin.

DR. COURTNEY GUSTIN: Good morning. My name's Lieutenant Commander Courtney Gustin and I'm part of the Defense Health Agency's Armed Forces Health Surveillance Division. I'm going to be presenting the results from the Department of Defense Global Respiratory Pathogens Surveillance Program and for the partners that contribute to this important effort on an annual basis.

Today I'll be presenting data on the 2021-2022 influenza season from our influenza surveillance network. Including an overview of the past three years of surveillance data with a snapshot of what's taken

place during the pandemic. Included here will be surveillance data from our partners in North America, South America, Europe, the Middle East, Africa, and Asia. As those other contributors, are analyses this year will be very limited in comparison to previous years due to both the low number of influenza cases captured through our surveillance program over the last several months, and pandemic prevention efforts.

I will provide a summary of phylogenic analyses developed by the U.S. Air Force School of Aerospace Medicine, or USAFSAM, and I'll share data on antigenic characterization for the season from the Naval Medical Research Center, or NMRC. And, in addition, I'll present mid-year estimates of vaccine effectiveness developed by the Armed Forces Health Surveillance Division Epidemiology and Analysis Branch. Finally, we'll review DoD's vaccine strain recommendations.

I'll start off with an overview of influenza surveillance within the DoD. Flu surveillance is included as part of the DoDs Global Respiratory

Pathogens Surveillance Program, which is managed out of the Global Emerging Infection Surveillance, or GEIS, Branch at the Armed Forces Health Surveillance Division. The GEIS branch is a DoD asset dedicated to the surveillance of infectious disease primarily, but not exclusively, within the military community. Our influenza surveillance program extends to over 400 locations in 30 countries through the work of DoD laboratories across the globe.

In addition to monitoring U.S. military personnel, our partners have relationships with foreign governments, including ministries of health, ministries of defense, and academic institutions. Which provide disease surveillance data on local, national populations. Our laboratories have extensive characterization capabilities, including cell culture, PCR, and sequencing capabilities. On average, approximately 30,000 respiratory samples are collected and analyzed each year within our network. We also have access to extensive health records for active duty military personnel, which are typically an important

source of data for monitoring influenza within DoD and conducting vaccine safety and effectiveness studies.

I'd like to briefly show where GEIS-supported influenza surveillance is active. The GEIS network is spread across all six geographic combatant commands and multiple laboratories conduct influenza surveillance routinely. One of the core GEIS laboratories, USAFSAM, has a particularly wide geographic footprint. And surveillance for influenza across many sentinel sites in the US1, Europe, and locations in the Indo-Pacific region. Testing for influenza declined significantly in 2020 and continued that trend into 2022 in the midst of the COVID-19 pandemic. Over the next several slides I'll present data on influenza subtypes detected by several of these GEIS network partners.

I'll reiterate again that influenza surveillance has been impacted significantly at these sites. Restrictions and lockdowns resulting in reagent shortages, shipping delays, and staffing reductions have impaired normal surveillance activities in an environment where many resources were being shipped to

COVID surveillance and where flu rates were already diminished by the public health measures implemented in response to the pandemic. Although surveillance efforts for DoD on the next few slides were lower than normal, influenza was detected in all the global combatant commands for the first time since 2020. Some notable regional examples include installation-wide influenza A outbreaks in North America, frequent detection of influenza A and B, including H1N1 in West Africa, and persistent influenza in Nepal. So you'll see this impact in the coming slides as I present our data region-by-region.

On the following subtype circulation charts, the MMWR week is along the X-axis, and the percentage of positive samples is along the secondary Y-axis on the right-hand side. The number of specimens submitted is along the primary X-axis on the left-hand side. Three years of data are shown starting with week 40 of 2019 on the left side of the X-axis to the most recent data for 2022 on the right side. Different colors of the bars indicate the different influenza types and

subtypes. This graph represents surveillance data for military members, including recruits, and military dependents residing within the United States, along with select civilian populations near the U.S./Mexico border.

Influenza A (H3N2) has been the dominant subtype detected in North America after an extended period with little to no influenza activity detected. For the DoD, some of this activity has been localized to specific areas of the United States, including Maryland, Georgia, South Carolina, Illinois, and the U.S./Mexico border, and has been outbreak-associated. The data are well-aligned with data from the WHO and provide more typing information for key DoD populations.

Moving on to South America, the surveillance data here comes from U.S. military and civilians as well as local military and civilian populations within Peru, Panama, Paraguay, Columbia, and Honduras. While the WHO covers much larger regions, including temperate South America, tropical South America, and Central

America and the Caribbean, the surveillance data from DoD is consistent and shows that the most recent influenza detected is primarily limited to influenza A (H3N2). Looking now at Europe, this graph represents surveillance data from military members and their dependents residing in 10 countries in Europe. This seasons influenza activity is still quite low. The few positives that were detected have been influenza A (H3N2) and influenza A un-subtyped. Much of the sampling for this region was out of Italy, Germany, and Georgia, which limits the generalizability of this findings and likely explains the lower counts and positivity compared to the WHO data in most recent months.

Moving on to our surveillance in Asia. These data represent U.S. military personnel and civilians as well as select local national populations within a large number of Asian countries. The DoD was able to provide key data during the pandemic for a number of countries compared to what we see with the WHO. Moderate levels of influenza A H1N1 and H3N2 and

influenza B circulated in 2020 and 2021. There was sustained influenza activity in Nepal for several months, which was driving the DoD data shown here more recently. The large number of influenza B detection shown in late 2021/early 2022 confirms surveillance activities where the DoD does not have a significant infectious disease surveillance presence, such as China, Sri Lanka, and India.

Now, looking over at the Middle East, this DoD graph represents surveillance data from U.S. military and civilians as well as select local national populations within eight countries in the Middle East. The majority of the data reflects sampling from Egypt and Jordan for the most recent season, with relatively little data from Afghanistan, Bahrain, and Kuwait. Which may explain the discrepancies between the two graphs. Influenza remained low in this population in the region. There was some influenza A activity detected, but otherwise, levels stayed low.

Moving on to East Africa. The DoD surveillance in East Africa comes from foreign military

and civilian populations in Kenya, Tanzania, and Uganda. Influenza activity was present throughout the pandemic, and levels remain steady across the three countries with periodic spikes in Kenya and Uganda. Influenza A (H3N2) was the predominant type detected, while influenza B was also circulating at low levels. The DoD data is slightly inconsistent with what the WHO data show here, although the number of countries surveilled by the WHO is larger than DoD. WHO data show low levels of influenza A (H1N1) circulating in Tanzania, which is a region where DoD only reviews a few samples per week.

Finally, looking at West Africa, the DoD surveillance data presented here primarily comes from foreign military and civilian populations in Ghana. When compared with the surveillance data from the WHO it's clear that they are consistent with respect to types of influenza in circulation, and timing. The data suggests that Ghana's a good surveillance proxy for the region for DoD. Moving forward here, at the Naval Medical Research Center, NMRC, some of the

current flu samples from USAFSAM were tested for antigenic reactivity against reference Antisera shown.

The highest dilution of Antisera that showed 50 percent neutralization against each sample by HINT assays is shown. All samples showed high reactivity to Antisera against A/Darwin/9/2021 and A/Darwin/6/2021, the Southern Hemisphere 2022 (H3N2) vaccine strain. Data from the previous slide was analyzed by a cartography program to generate the antigenicity map shown here. All but one sample clustered together and are antigenically similar to A/Darwin/2021, cell- and egg-based. Sample 12, the purple drifts from the cluster. We will also see this is the phylogenetic tree that's presented later.

And this slide shows the metadata from the samples, illustrating two different subgroups, D53G and D53N. The three substitutions in the sample number 12, S156H, S205F, and A212T appear to have an impact on antigenic reactivity. So, in summary, our influenza surveillance data from our global lab partners is still limited for this flu season. North America influenza A

(H3N2) has been the dominant type. In South America positivity for H3N2 has increased in recent months. Europe has seen low levels of influenza. Asia has had moderate activity lately with H3N2 and influenza B. In the Middle East we've seen low levels of primarily influenza A detected. In East Africa moderate influenza has been noted with all subtypes detected. And West Africa is one of the only regions with H1N1 circulating.

Moving on now I will discuss the phylogenetic analysis completed this year by the U.S. Air Force School of Aerospace Medicine, or USAFSAM. Looking at the geographical distribution, sequences from 450 total influenza positive specimens were collected with one A(H1N1)pdm09 from the United States, one B/Yamagata from the United Kingdom, and 448 A(H3N2) collected from Germany, Italy, Peru, the United Kingdom, and the United States. Specimens were collected as part of the DoD Global Respiratory Pathogens Surveillance Program at USAFSAM in addition to specimens contributed by Eglin Air Force Base, Landstuhl Regional Medical

Center, and specimens and sequence provided by the Naval Health Research Center in San Diego, and the Naval Medical Research Unit 6 in Peru.

All 448 of the A(H3N2) hemagglutinin sequences collected were in clade 3C.2a1b.2a2 with 405 sharing the substitution D53G/D104G/L157I/S262N and K276R. And 27 shared D53N/D96S/I192F, and N378S. Four viruses shared S205F and A212T, which are circled in yellow on the tree. One of these viruses was antigenically characterized and showed antigenic distinction from reference virus strains and the other surveillance strains sharing either D53G or D53N. The 2021 Northern Hemisphere vaccine strain is marked by an orange star.

The 2021/2022 Northern Hemisphere vaccine strain is marked by a red star, and the 2022 Southern Hemisphere vaccine strain, a 3C281B.2a2 virus, is marked by a pink star. N96S causes the addition of a glycosylation motif and two individual losses of glycosylation motifs occurred. A/Maryland/02/2021 a clade 3C2a1b.2a2 reference virus, sharing the D53 substitution group, was most closely related to the

circulating strains observed. Circulating A(H3N2) clades over the last three years are shown here. Illustrating much higher genetic diversity. The 2018/2019 and 2019/2020 season. Extremely low circulation and diversity in the 2021 season, and an increase in circulation for the 2021/2022 season. Although all the strains in 2021/2022 season fall under clade 3C2a1b.2a2, an increase in diversity from last season is also observed when considering the emerging subgroups. Distribution of the previous two vaccine strain selections are shown in the text boxes color coordinated with the associated clade of each strain.

Neuraminidase sequences were available for 428 of the influenza positive specimens. The NA phylogenetic tree is very similar to the HA phylogenetic tree, indicating a similar genetic trajectory and relation of circulating strain NAG to vaccine and reference strain NA. The substitution S329N caused the addition of a glycosylation motif and a minor branch location in the tree, which corresponds to virus and sharing the D53N HA substitution group.

A/Maryland/02/2021 once again falls well within the majority of the strains represented.

So, to sum up, the one influenza A(H1N1)pdm09 specimen sequence was in clade 6B.1A-5A.1 and contains the substitutions R113K and H399N, which are shared with the 5A.1 reference strain. The reference strain A/Pennsylvania/02/2021, the one influenza B specimen available for characterization was a Yamagata lineage virus in the say clade Y3 that has been circulating for many years and is well-covered by B/Phuket/3073/2013. All influenza A(H3N2) specimens were in clade 3C.2a1b.2a2 with 94 percent sharing the substitution D53G/D104G/L157I/S262N and K276R.

Now I'd like to review the vaccine effectiveness estimates performed by our Armed Forces Health Surveillance Division Epidemiology and Analysis Branch. To start off I'll first mention what typically comprises our annual vaccine effectiveness analysis. We usually have three partners that contribute to this effort, the Armed Forces Health Surveillance Division satellite at USAFSAM usually provides vaccine

effectiveness analysis for our active duty beneficiaries within the Department of Defense and the Naval Health Research Center provides data for vaccine effectiveness in military basic training. However, the small number of positive results available for those partners prevented any kind of meaningful analysis of vaccine effectiveness in this population, so I will not be presenting those results today.

The Armed Forces Health Surveillance Division Epidemiology and Analysis branch conducts our vaccine effectiveness analysis for active duty personnel. Unfortunately, we do have some data to present for that population, which I will discuss on the next few slides. The study design for this analysis is case/test negative control design on active component personnel from all the military services, including those stationed within the continental United States, or CONUS, and those stationed in foreign locations, OCONUS, during the September 1, 2021, to February 12, 2022, time period.

These cases were lab-confirmed by either

positive rapid test, RT-PCR, or culture assays. Test negative controls were those that presented for care, tested negative for the flu by either RT-PCR or culture assay. Those that were negative by rapid tests alone were excluded from the analysis. Models were adjusted for sex, age, category, prior vaccination, and month of diagnosis. I'll present both accrued vaccine effectiveness for both influenza A and influenza B in the next slide. Inactive influenza vaccine was the only vaccine type used in these study subjects. It's also important to note that our active duty population is a highly vaccinated population, as the flu vaccine is compulsory for active duty personnel. So 85 percent of the study subjects had been vaccinated for flu within the previous five years.

We had 1,303 influenza A and 165 influenza B cases to include in the analysis. The higher proportion of cases were identified in December, 55 percent, with test negatives spread out over the entire study period. Our breakdown by age group of both cases and controls is shown here. U.S. military population

is relatively young compared to the general U.S. population, which will limit the ability to generalize these results to the broader U.S. population. Here are the results of the analysis showing overall vaccine effectiveness and then for both influenza A and B. So, in summary, the overall mid-season vaccine effectiveness was 36 percent, but do remember that this is the relatively young, active duty military population only. It was somewhat higher for influenza B at 59 percent, indicating moderate protection and then notably lower at 33 percent for influenza A.

Here are notes on vaccine strain recommendations. The A(H1N1)pdm09 strain recommendations inhibit 6B1A5A.2 viruses well and 6B1A5A.1 viruses less well, however, we feel that our one 6B1A5B.1 virus from Europe is not representative enough to agree or disagree with this recommendation. The A(H3N2) strain recommendations inhibit 3C2A1B.2a2 well, as also suggested by our antigenic data on the overwhelming majority of our viruses. The slight antigenic distinction of a virus with the substitution

S205F and A212T representing a small number of viruses from Europe will likely have little impact. We do not have any B/Victoria sequence data for the 2021-2022 season and therefore cannot comment on that strain selection. The B/Yamagata strain recommendation inhibits Y3 virus as well, however, we feel that our one B/Yamagata sequence is not representative enough to agree or disagree with that recommendation.

I'd like to acknowledge our colleagues at the Armed Forces Health Surveillance Division as well as our partner labs, we are incredible grateful for your contributions to this presentation and in completing all of our surveillance efforts. And we have a second slide because we have a lot of great colleagues. And that concludes my presentation, so I'm open for questions.

Q AND A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Courtney, for this presentation. Michael is going to put me back as presenter, and here we go. I have two committee

members with questions, beginning with Dr. Shane. Dr. Shane?

DR. ANDREA SHANE: Yes, thank you so much, and thank you for that very helpful and informative presentation. I just had a question, you mentioned that the surveillance included dependents of the armed forces members. I was wondering if you have any data on that specifically, with focus mostly with respect to vaccine effectiveness or if you don't have that information? Thank you.

DR. COURTNEY GUSTIN: Sure. Normally that is part of the presentation, but this year those partners had reported that they didn't have enough data to do a meaningful analysis of vaccine effectiveness in the dependent-only population.

DR. ANDREA SHANE: Thank you.

DR. HANA EL SAHLY: Dr. Courtney, is there any severe disease or hospitalization cohorts, or is it mostly out-patient mild disease?

DR. COURTNEY GUSTIN: I don't have that data close at hand, I'd have to follow-up with that, and I

can get back to you later today on that.

DR. HANA EL SAHLY: Second in line, Dr. Offit. Dr. Offit?

DR. PAUL OFFIT: Yes, thank you for that clear presentation. Hana, you just asked my question, I just wanted to know what we had knew about vaccine effectiveness from mild, moderate or severe disease, which is really data we need to get, so hopefully we'll get those data soon. Thank you. Thank you, Courtney.

DR. COURTNEY GUSTIN: Sure, I'll follow-up with our partners and see if I can, I'll get it to the hosts of the conference today as soon as I can.

DR. HANA EL SAHLY: Thank you. I do not see any raised hands, so I want to thank Dr. Courtney for taking the time and presenting this data to the committee. Our next presenter is Dr. Manju Joshi (audio skip) in Quality and Office of Compliance and Biologics Quality at CBER. Dr. Manju Joshi is going to go over the candidate strains and potency reagents.

CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS

DR. MANJU JOSHI: Thank you, Dr. El Sahly. My name is Manju Joshi, and I am from the Division of Biological Standards and Quality Control in Office of Compliance and Biologics Quality at CBER, FDA. In today's presentation I'm going to be covering the WHO recommendations for 2022-23 Northern Hemisphere influenza vaccine. I'll give you an update on the situation with the availability of potency reagents for each of the recommended strains. I'll give a little bit of comments about how we're planning for the dispensing of vaccines for 2022-23 season. And, since this is my chance to address, and I know there are a lot of vaccine manufacturers that are also listening in, they're on this meeting, I'll just put some general remarks which will be not so much for the committee members, but to the general audience and in particular the vaccine manufacturers.

So, for influenza A of H1N1 type, the WHO recommended viruses for 2022-23 Northern Hemisphere

season vaccine is same as it was for 2021 Northern Hemisphere season and also the same virus was recommended for 2022 Southern Hemisphere season. The recommendation is being for egg-based vaccines A/Victoria/2570/2019 H1N1pdm09-like virus. But for cell culture- or recombinant-based vaccines the WHO recommendation is the A/Wisconsin/588/2019 pdm09-like virus. In the interest of the time, I haven't listed all the candidate vaccine viruses, they are available for each of the groups. But I have provided the information so that anybody interested can look up all the different viruses available with the WHO site.

And, so, here I'm going to give you an update on the status of the various potency reagents who are testing of A(H1N1)pdm09-like component of 2023 vaccine. Let me make it clear, this is based on if the committee approves the recommendation which provided by WHO, we have the reagents available for testing of vaccines. There have been several viruses and reassortants made available and at CBER, since we do have, for the (inaudible) vaccine, we had prepared the reference

antigen and antiserum for A/Victoria/2570/2019 IVR-215 reassortant and those reagents are available from CBER. Available from our collaboration partners, which are from TGA and NIBSC had also prepared these reagents and they are available from them as well.

Similarly, from any manufacturers who are interested in using different reassortant from the same group or A/Victoria/1/2020, our partners at NIID have made these reagents available.

As far as H1N1 components for the cell platform is concerned, CBER had prepared the reagents for A/Delaware/55/2019, which was one of the recommended virus. And those both reference antigen and antiserum are available.

Last year, cell platform people had decided to use another virus from H1N1 component, which is A/Washington/19/2020 virus from the same group. We did make a reference antigen standard and made it available for use. Similarly, for the recombinant platform, they had chosen to use A/Wisconsin/588/2019 from this group and CBER has made the reagents available for them as

well.

So, this is just to give you an idea that if this strain is selected by committee, that the reagents for each of these are available. Coming to the influenza A of H2N2 type. WHO recommended virus for 2022 Northern Hemisphere season vaccine is different from that which was recommended last year for 2021-22 Northern Hemisphere season. But it is same for 2022 Southern Hemisphere season.

So the recommendation for egg-based vaccine is A/Darwin/9/2021(H3N2)-like virus, and that for cell culture- and recombinant-based vaccine it is A/Darwin/6/2021-like virus. Again, the candidate vaccine virus list is available at the WHO website, shown here on my slide.

If Committee were to approve this strain for inclusion for the US vaccine, the status of the reagents is as follows. This strain was recommended for Southern Hemisphere campaign. We, at CBER as well as (inaudible) have worked to produce reagents for Southern Hemisphere campaign and exclusive strains

continuous reagents will be made available. At CBER, we had prepared reference antigen reagents and PCR for A/Darwin/9/2021, for a cell (inaudible) reassortant. And those, out of the interest of time, again, I'm not reading all the lot numbers or anything, but the reagents as shown on the table are available.

Our partners, NIBSC has also prepared the similar reagents for -- NIBSC went ahead and prepared reagents for A/Darwin/9 IVR-228 reassortant if anybody had to use. And, similarly, reagents for A/Darwin/6 IVR-227 reassortant for all egg platform are the three so far I have said but made available by other partners. We here at CBER prepared reference antigen reagents and calibrated it for A/Darwin/11/2021 for the cell platform aspect.

And I just wanted to point out that we were closely partnered with other collaborators, so that's why this reagent planning is done at a group just to make sure as many reagents can be prepared and there is more choice of reagents for the different strains are selected.

Coming to the influenza B from B/Victoria lineage. WHO recommended virus for the upcoming season for trivalent and quadrivalent vaccines, different from what was recommended for '21-'22 Northern Hemisphere season. Yet, again, it is same as 2022 Southern Hemisphere season.

Then, WHO recommended that for egg-based vaccines, B/Austria/1359417/2021 from B/Victoria lineage, be the candidate virus. And for cell culture and recombinant was the similar virus recommended. If this was to be included in the vaccine, again, the status of the reagents for vaccine testing are listed here in the table.

Since this was recommended for Southern Hemisphere campaign we had worked to prepare the reagents. Here at CBER we work to prepare reference antigen reagents and antiserum for B/Michigan/01/2021 for egg platform. And those antigens Lots are available and even antiserum are available. Similarly, our partners TGA and NIBSC have prepared the reagents for B/Austria reassortant BVR-26 and those are

available from them as well.

Again, in our domain, we have worked to prepare a cell reagent for B/Singapore/WUH4618/2021 strain, and the reference antigens are 2115 is available along with the antiserum for testing of this component in cell-based vaccine, if it's selected.

Coming to the influenza B, which I call the second B-strain, which is always from the B/Yamagata lineage, the WHO has recommended that virus for '22-'23 Northern Hemisphere season quadrivalent vaccine is the same as what was last year. It was the same in 2022 Southern Hemisphere season and as all the previous presentations have pointed out, that this strain has been going on seems like forever.

So, for egg-based vaccine, the WHO recommendation for the quadrivalent, the second B-strain would be B/Phuket/3073/2013 from Yamagata lineage for both -- this is the same for cell culture and recombinant vaccines as well. And you can check the list of all the candidate vaccine viruses from this group at the WHO website.

Taking a quick look at what is the situation of the reagents that are available for testing of this component of the vaccine. So, CBER has the reagent available for B/Phuket for egg-based vaccine, both antigen and antiserum are available, even the reagents. Since this strain has been going for so long, the others ERLs, NIBSC, TGA, and NIID have reagents available as well with them.

For the reassortant BVR-1B for the B/Phuket strain, TGA has prepared reagents and they have been made available. We at CBER have worked and prepared the reagents for the B/Singapore/INFTT-16-0610/2016 which is for the cell platform. And represented in an antiserum for testing this component is cell-based vaccine is available.

In addition in that, the manufacturers of cell platform had chosen to use B/Utah strain from the same group and CBER has provided those reagents as well. We have even prepared a reagent for the B/Phuket for recombinant platform, and those reagents are also available from CBER. So, if committee approves this

strain, again, the reagents are in place.

Now question comes how are we ready for preparing and calibrating of any new reagents needed? As I pointed out, since the strain recommendation for the B/Victoria reagent as seen are the same as Southern Hemisphere campaign, we have prepared reagents for those two for egg and cell platform. So now we are ready to work with ERLs and the manufacturers to prepare and calibrate the reagents required for potency testing of A/Darwin-like component in recombinant vaccine as well as for B/Austria-like component recombinant vaccine if these recommendations are finalized and the recombinant vaccine manufacturers will acquire these reagents.

In addition, we in the DBSQC at CBER are ready to calibrate any reagents, any new reagent, if a manufacturer chose to pick up a new reassortant or new strain for their manufacturing company. So we are ready to take on that and proceed with it.

Coming down to -- I think this is not interest to the committee as such, but I'm just putting it out

mainly for our manufacturers who are listening on this call. And we would like the manufacturers to provide us the following information as I have shown here, which includes the strain name, reassortant or vaccine virus they are planning to use in manufacturing. Since there are several reagents available, which reagent referencing antigen and antiserum and their supplier they're trying to acquire.

I have considered that having this information is extremely important for us to plan our laboratory activities. All of us were planning the work around reagent calibration. Depending on what reagents are getting used, we have to think about importing reagents from other ERLs if they are the one manufacturer chooses to use. And there's a big bulk of activities which involve the testing of (inaudible) which they call monovalent bulk testing and eventually, the Lot release testing. So, for a smooth operation of the whole process of vaccine testing, we would like manufacturers to send us this information so that it helps us in planning.

Continuing with some more comments. I want to let manufactures know that only CBER-authorized reagents should be used to test potency of vaccines marketed in US. So that's the reason why it would be very helpful if you just consulted us, let us know what your plans are, and then we can move forward with it.

When it comes to submitting the samples for monovalent samples, they should be submitted to Division of Biological Standards and Quality Control. Please email me, my email address is here, regarding dispatch of sample and test results. And always cc on the email my lab chief, Dr. Shahabuddin, his email is included here as well.

And if manufacturers have any inquiries regarding CBER Reference Standards and Reagents about availability, shipping, please contact CBER Standards at the email address provided here.

And, one last thing I would like to add is, please send us -- manufacturers, we would appreciate it if you can send your feedback, comments on the availability, suitability and useability of reagents we

are providing and any other aspect of our services to our Influenza Mailbox, the address is CBERinfluenzafeedback@fda.hhs.gov. We monitor that mailbox and if there are any questions or any communication is needed we can do that as well. So, thank you, and I can take any questions.

Q AND A SESSION

DR. HANA EL SAHLY: Thank you. Dr. Joshi. Are there any questions for Dr. Joshi? I see none, but I want to thank you for all the hard work getting the laboratory references and potency reagents ready for this big task.

DR. MANJU JOSHI: Thank you.

DR. HANA EL SAHLY: As a follow-up to the presentation by Dr. Groshskopf this morning, Dr. Groshskopf would like to provide additional comments. Dr. Groshskopf? Dr. Groshskopf, please unmute yourself and turn your camera on.

DR. LISA GROSHSKOPF: Okay, I'm sorry. I

think I'm unmuted now, yes?

DR. HANA EL SAHLY: You are.

DR. LISA GROSHSKOPF: Okay, thank you. In checking with my surveillance colleagues regarding the question concerning surveillance of coinfections, I'm told that in FluSurv-NET and COVID-NET they do look for patients with hospitalizations reported in both systems. And they also look through virologic surveillance data from public health labs to pull specimens that got tested for both flu and Sars-CoV-2. So there is some following of such coinfections within those systems.

DR. HANA EL SAHLY: Great. So I guess this data will be forthcoming in application or MMWR later maybe?

DR. LISA GROSHSKOPF: I (audio skip).

COMMENTS FROM MANUFACTURER REPRESENTATIVE

DR. HANA EL SAHLY: Thank you for the follow-up. Next is Dr. Beverly Taylor. Dr. Beverly Taylor is

head of Influenza Scientific Affairs, WHO and IFPMA Lead Seqirus, a CSL Company. Dr. Taylor will provide the influenza vaccine manufacturer's perspective.

MR. MICHAEL KAWCZYNSKI: Hold on, Dr. Taylor, there we go.

DR. BEVERLY TAYLOR: Hi, can you hear me okay?

MR. MICHAEL KAWCZYNSKI: Yes, we can.

DR. BEVERLY TAYLOR: Okay. Thank you very much. My name is Dr. Beverly Taylor, I work for Seqirus Vaccine, but I am giving this presentation on behalf of influenza vaccine manufacturers. Just for your information, IFPMA is International Federation of Pharmaceutical Manufacturers and Associations. And it's the international industry association based in Geneva.

I'd like to thank the VRBPAC committee for giving me the opportunity to provide the industry perspective today. And I'd like to point out that this summary was prepared from a variety of public sources, and it has been reviewed by Seqirus, GSK, Sanofi, and AstraZeneca. Okay, and my disclosure statement is I am

an employee of Seqirus, and I do own shares in the company.

So the key messages in the presentation today are the key components of a successful vaccination campaign, or vaccine manufacturing campaign. Having a look at the influenza surveillance during the COVID-19 pandemic, we've seen some of that today, but just reinforcing that. The strain changes that we had for the Northern Hemisphere '21-'22 season and the reagents supply for those strains. An overview of the manufacturing campaign timelines. The continued challenges that we see due to the COVID-19 pandemic. I also want to give an update on the Nagoya Protocol.

So what do we need for a successful influenza vaccination campaign? So, obviously, we want to have the vaccine as well-matched as possible to the circulating influenza strains. And that's why it's so important for us to have the ongoing and robust surveillance that provides WHO with that, and VRBPAC with that information. We also need the timely availability to vaccinate before the upcoming influenza

season, so that means that we, as manufacturers, have to have our vaccines ready in plenty of time for that to be achieved.

And that, in turn, means that we need the supply of the candidate vaccine viruses and the potency assay reagents in good time. We also need sufficient vaccine doses to support the recommendations in increasing immunization rates, and for this we need to be able to evaluate the candidate vaccine viruses and work out which viruses work best in our manufacturing platforms. And that we have some time to optimize the yields. And all these factors feed into the influenza vaccine strain selection, and that strain selection impacts the timing of our supply. I know we've seen a lot of surveillance slides and we can see that the impact that the COVID-19 pandemic had on flu circulation, but I think it's just worth looking. I took the same week in 2020 and 2021, so week five of 2020, we had 25, in the U.S., approximately 25,000 positive samples for influenza. Compare that in 2021 week five and we have less than a hundred. So that

just shows you the impact of the measures that we took to control COVID and the COVID pandemic had had.

However, it's important to say that there were still pockets, as was discussed before by committee, in Southeast Asia and Africa, and there were antigenically distinct viruses detected. So there was still a need to obtain the composition of the vaccine even though flu circulation levels were so low. And we did continue to see the viruses evolving, so there are just the next strain graphs that have been shown by Dr. Wentworth previously. And you can see the activity of the viruses is continuing, except with the Yamagata virus, as Dr. Wentworth indicated, we have not seen any viruses. Although I was very interested to hear in the previous presentation that there was one B/Yamagata detected, I think it was in Europe. But, from the WHO surveillance, no B/Yamagata viruses have been confirmed since 2020.

So, in the last year, the VRBPAC committee recommended the formulation for the seasonal vaccine, and there were two changes. So we have a change to the

H1N1 to the A/Victoria/2570/2019 and to the A/Cambodia, I'm not going to say that number, 2020, that was for the egg-based. And cell- or recombinant-based we had recommendations for A/Wisconsin/588/2019 or the A/Cambodia for the H3N2. An also, for the trivalent influenza vaccine, the committee recommended that the B/Victoria lineage virus be used and obviously there were two strain changes from the previous season.

Regarding the supply of the potency reagents for this Northern Hemisphere season. CBER again confirmed that they would accept TGA and NIBSC reagents for testing of egg-based vaccines, provided that we, as manufacturers, supplied them with that information at the beginning of the season, and specified which reagents that we were going to use. The timing of the calibration dates are given here, there were a number of the calibrations of the reagents were done, the calibrations were done for the Southern Hemisphere, and so they were available late 2021. And then, for the A/Wisconsin recombinants, the calibration date was the end of May.

And if we look at the supply of the H3N2 potency reagents, we can see that for all of the candidate vaccine viruses that were being used by manufacturers, whether that be egg, cell, or recombinant, the calibration dates for the reagents were in late May or in June. Which really is within the normal timeframe that we would expect the calibrations. I just want to say thank you to CBER and the other ERLs because despite the ongoing concerns about reduced number of flights, issues with international couriers, the ERLs prioritized the calibration of reagents and the timing of the calibration values. Which are essential for us to be able to formulate and release our final vaccines, was similar to previous years. And I just want to thank Dr. Joshi for the presentation that she just gave and the information that she provided to the manufacturers. And we are prepared to supply the information that she outlined in the normal format that we do. So thank you very much for that, Dr. Joshi.

So we made the point before that it takes

teamwork to get influenza vaccines across the finish line. And we have used before a relay race analogy. And we say that the first runner is at full speed, and this is the WHO collaborating centers, the ERLs, the reassortant labs are going at full speed to supply us with the candidate viruses. And then the receiving runner starts running before the handoff. So we, as manufacturers, are starting to produce at-risk before the candidate vaccine virus or the virus selection has been made, so that we are maximizing our chances to supply within the expected timeframes. And then we see the runner is at full speed at handoff.

And, so, we've already started manufacturing at-risk and we're also preparing receiving the candidate vaccine viruses and we're ready to use the new strains and get ready for formulation. And throughout the race there needs to be strong planning and good communication. And we do have bi-weekly WHO industry teleconferences. We also have now in place a cross-functional working group influenza hub, which is hosted by NIBSC in the U.K., and that means that we can

get real-time information on candidate vaccine viruses and where reagent preparation is up to. Rather than just waiting for the bi-weekly meetings. So that has been incredibly helpful in our planning.

We also have additional challenges for influenza. We don't only have one baton being passed, we have multiple batons, we have candidate vaccine viruses, we have reagents, we have different vaccine types. And there are also multiple providers, so we work with the WHO collaborating centers, the essential regulatory labs, the reassortant labs, and all these pieces have to come together in order for us to have a successful campaign. So we always have hurdles during the manufacturing campaign, and the hurdles in the Northern Hemisphere 2021-'22 campaign were two strain changes. I mean, this is not unusual, it's part of working with influenza, we expect this. Every time there is a strain change, there is lots of work to do. We have to qualify the new candidate viruses, we have to make annual submissions to update the viruses. So strain changes do add to the workload.

We've also seen Nagoya Protocol issues, which I'll discuss in a bit more detail in later slides. We had challenges with materials and component supplies this year. And that's because, for good reasons, a number of materials and components were redirected towards vaccines for COVID-19. However, we have to understand that the influenza virus was still very important and that we still needed to have the materials and components that we needed to deliver the flu vaccine on time. And then with the ongoing impact of the COVID-19 pandemic on transport and freight.

So, you've seen this slide before, but this is our, the annual influenza vaccine manufacturing timeline for U.S. supply. So you can see, if we start at the left-hand side of the graphic here, you can see an orange box where we start production at-risk. So we will start, prior to the strain recommendation, as early as January. So we have a couple of months before the VRBPAC recommendation where production starts at-risk. And, this again, is where the surveillance and the information sharing is really important because in

order that we don't lose the benefits of starting production early and at-risk, we need to choose a strain that is least likely to change in the recommendation. So that's why we're constantly monitoring the surveillance and trying to get as much transparency with the information as possible.

Once the strain selection's been made, we then go on to produce the other strains. Each strain is manufactured separately and then, when we have manufactured material from each of the strains, we can then, and the reagents are available, we can then formulate the final vaccine and then obviously fill and package. So, a Northern Hemisphere campaign, about 500 million doses are produced and distributed globally. It takes about six months to get to the first dose currently, and eight months to the last dose. So it's a very tight window and any delay or any reason why we can't move forward will impact our ability to start in time.

So, Dr. Wentworth mentioned the one year that we had a delay of a month for an H3N2 recommendation,

that certainly put pressure on this timeline. We could still produce some of the other strains, not at-risk, but we could still go ahead and produce the other strains, but until we had the H3N2 strain produced we weren't, and the reagents, we weren't able to formulate the vaccine. So understanding why the delay was needed, but it definitely does have an impact and put pressure on the system. And the other thing I want to highlight from this is it's really important for manufacturers to get early demand planning. So we need to plan how much we're going to make for the campaign and at what point we need to start the production at-risk if we're to ensure sufficient supply of the vaccines for the season.

This graph is just showing the U.S. influenza vaccine distribution and we have this current season as well as the previous two seasons. The purple, the light purple line is showing the vaccine distribution for the 2019-2020 season. The green line at the top is showing the 2021-'22 season, sorry, no, that's the season before, 2020-'21. And then the blue line, which

is difficult to see because in the later weeks it falls under the 2019-2020 line, that is actually this current Northern Hemisphere. And I think we're up to about 174 million doses distributed for this season. So we responded, as manufacturers, in the Northern Hemisphere 2020-'21 season with, it was actually about an 11 percent increase in the number of doses versus the previous season. And that was because of the increase in demand, because of the COVID pandemic, and people were afraid of the twin-demic, and so, demand went up and manufacturers were able to respond to that.

Demand for this Northern Hemisphere season was lower, but it was similar to the Northern Hemisphere 2019-'20 season. However, we have seen the flu vaccination rates have been slower this year and were, at least initially, lower overall than the previous two seasons. So the graphic in the top right-hand corner is just showing it's got years on the X-axis and millions of doses on the Y-axis. And you can just see that over the years the total vaccines distributed has gone up, but it's all got to fit into that tight, tight

timeframe for that manufacturing window that we have. So, even though the number of doses have gone up so significantly, we've still been able to deliver the vaccines within that window.

So we're continuing to see challenges due to the COVID-19 pandemic this Northern Hemisphere season or leading up to the selection of the viruses for this season. Despite increased testing by the National Influenza Centers, we saw only low levels of influenza detected. There were pockets of activity, as has been said, in Southeast Asia, in parts of Africa and China. But it wasn't clear that as things opened up that the viruses that were isolated in those pockets would be the viruses that would circulate more widely. So it made this decision very difficult. Different viruses were isolated in different regions, so, again, it was difficult to predict which one of those viruses would predominate for the Northern Hemisphere '21-'22 season. There were also a long number of available virus isolates for this season. And, again, for the Southern Hemisphere 2022 manufacturing campaign, which means we

have less viruses, candidate viruses, to select from and so, we have less choice in which ones we use on our manufacturing platforms and so we might end up with something that's less than ideal because we are not able to pick the best one for our particular platform.

Again, it's been said before, we saw no genetic sequence data or physical samples received for B/Yamagata viruses, and that's almost two years now. And, also, we continue to have a lack of clarity on Nagoya Protocol and access and benefits sharing status with a limited number of available viruses and some of those viruses coming from countries that have Nagoya Protocol legislation or national ABS legislation in place that puts more uncertainty around our ability to use those viruses in manufacturing.

I mentioned the supply chain challenges and material shortages due to the prioritization of materials for COVID-19 vaccines. And then, obviously, we're concerned about slower and reduced influenza vaccine uptake rates. I've just got a few slides on Nagoya Protocol. I realize that many people on the

call won't be as familiar with Nagoya Protocol or Access and Benefit Sharing legislation, so just a little bit of background. So the Nagoya Protocol on Access and Benefit Sharing is an international treaty which is supplementary to the Convention on Biological Diversity.

And it was adopted in 2010, and the objective is fair and equitable sharing of benefits arising from the utilization of genetic resources from a particular country and, therefore, contributing to the conservation and sustainable use of biodiversity. So the Nagoya Protocol came forth in October 2014, and that was after the 50th country ratified the protocol. The U.S. is not a signatory or party to the Nagoya Protocol, but that doesn't mean to say that entities and, including manufacturers, that operate from the U.S. could not be impacted by this legislation. So, under the terms of the Nagoya Protocol, genetic resources can be accessed subject to prior informed consent from the country of origin once mutually agreed terms have been reached.

And it's the responsibility of each party to decide how they address pathogens. So whether pathogens are included in that legislation or not. In many cases, pathogens have been included. And, to date, 134 countries have become party to the Nagoya Protocol, and many have implemented the ABS legislation, which could potentially impact pathogen sharing. And not only the physical samples, but also the use of digital sequence information or genetic sequence data from those pathogens. So, obviously, this impacts influenza. And the legislation differs in each country, which poses challenges when you're trying to interpret the requirements from that country. And the other point that is important to make here is the agreement to buy lateral, so it's between an individual manufacturer and the country. So, in the very tight timelines that we have for influenza, it's very difficult to meet those timelines if we have to negotiate prior informed consent and mutually agreed terms in a matter of months.

So, the current situation is that an

increasing number of countries have enacted legislation, whether that's a national legislation or Nagoya Protocol legislation, and in many cases this does include genetic sequence data. I have to say that most of the national influenza centers have continued to supply influenza viruses under their agreed terms of reference as part of the global influenza surveillance and response system, or GISRS, however, there's often a lack of legal clarity if the viruses can be used for vaccine manufacturing research or any commercial purposes. And this is having a big impact on our ability to use some of the candidate vaccine viruses and since September 2018, we've had in excess of 30 influenza viruses impacted by this type of legislation. I think we're up to 37 now.

And the graphic on the right-hand side here just shows, I know you can't read all the viruses impacted, but it just shows you which viruses we've got authorization to use, which we had tacit authorization to use, which required material transfer agreements, and then, the viruses listed on the right-hand side

with the red boxes are viruses that we never received authorization to use. And some of those are older viruses, but some, the top ones are more recent viruses. And, basically, we timeout if we don't get the authorization within a certain period of time. It's too late for the season and then, later on, the virus has moved on and so, some of these viruses become irrelevant.

But we had a particular issue for this Northern Hemisphere when the virus from Cambodia was recommended. There were delays in obtaining legal clarity on the ability for us to use the A/Cambodia for commercial purposes. Permission was given for non-commercial purposes, and it took about a month after the WHO recommendation to get clarity that this could be used in manufacturing. And this had a big impact on manufacturers because it impacted the timing of the decision of which viruses would be used by each manufacturer. It also called into question whether critical reagents would be prepared and made available to manufacturers. So, even if a manufacturer went

ahead and used the Cambodia strain, there was a period of time that we weren't sure whether the critical reagents would be prepared to support that.

And it was a very difficult situation, but the virus that was listed on the WHO website couldn't actually be used by manufacturers and we didn't get that clarity for, until a month later. And there was a possibility that manufacturers would have to change the strain that they used, and the possibility of batches being discarded. In one particular case, there was one example of a vaccine manufacturer that chose an alternative strain, but fortunately there was an alternative strain, from Tasmania, but the yields on some manufacturing platforms were lower and one particular manufacturer supplied 40 percent less vaccine doses because they had made the decision, a safe decision, if you like, not to have legal uncertainty, but it resulted in fewer doses being supplied to the market.

We did, as I said, eventually get approval from Cambodia for commercial use, but there is still no

written confirmation that no benefits are required. And in some countries where the legislation is now being enforced, it's very difficult for us to provide evidence that we have met all the requirements. So this does pose an ongoing risk to seasonal influenza vaccine supply, including for the U.S. market. So it's something that we have to be vigilant monitoring, but also try to improve the situation.

There have been frequent questions regarding the compliance of Nagoya Protocol on sharing the seasonal influenza viruses and often different stakeholders are facing similar issues. So the legal firm Covingtons, based in Belgium, the Belgium office, generates a report on the impact of Nagoya Protocol on seasonal influenza virus sharing based on interviews that they carried out with stakeholders. And this was done last year. And it included the current work processes in GISRS, the impact of Nagoya Protocol on national ABS laws, and some suggestions to overcome the challenges that we're currently facing. And the report was reviewed by a multi-stakeholder group at a meeting

held at NIBSC in the UK last July, with the aim of finding solutions to some of these Nagoya challenges, specifically for influenza.

And there's a general agreement to work towards a common approach to compliance with the Nagoya Protocol and national ABS laws. And we discussed this again at the January NIBSC meeting earlier this year. And we agreed to look at continuing communication with national authorities, particularly the Ministries of Health and Environment, because they're the ones that the Nagoya Protocol (inaudible). So they're the ministry that are involved in this type of legislation.

And to really have the benefits of the GISRS system recognized and see how that fits with the benefit systems in the Nagoya Protocol. WHO are also in the process of developing a toolkit for the National Influenza Centers to use with their Nagoya Protocol National Focal Points, trying to explain how the GISRS system works and to recognize the benefits that GISRS brings to the individual countries, and to try and have those benefits recognized under the legislation.

There is also something called the Seasonal Influenza Material Transfer Agreement that has been used in some cases, we're looking to see if that could be used more broadly. And, then, a review of the Terms of Reference for the National Influenza Centers. So these are things that we think that we can, that deal specifically with influenza that might ease the situation. Well, I guess our message today is that the bedrock of global health security is the swift, certain, and unencumbered access to pathogens and their genetic information. And I think this has been talked about a lot because of the COVID-19 pandemic. A lot of the things that are being discussed and lessons learned are all talking about rapid sharing of pathogens and their genetic information. And pathogens know no borders, it's not like a plant that's growing in a country. For me, I think of pathogens as tourists passing through countries, so putting a border around a pathogen and accessing the benefits is very difficult. And sometimes it won't be easy to say that the pathogen started in that particular country. The timely sharing

of samples and genetic information is absolutely essential if we're going to respond to potential epidemics and pandemics.

And the inclusion of pathogens, including influenza, under this national ABS legislation is already causing significant delays and disruptions. As I said before, the bilateral negotiation approach is just time consuming, and we simply don't have the time when we're trying to respond to some of these public health emergencies. And legal certainty regarding the status of pathogen sharing under ABS legislation is necessary and we feel that clear exemption of pathogens will be the most effective way forward, but as negotiations are going on and the landscape complexity is increasing, we're not sure if that's going to be a possibility. There are a number of things being discussed that impact the access and benefit sharing. We have the PIP Framework for pandemic influenza, which there's talk about that being expanded. Currently it just covers (inaudible) samples, that could be expanded to cover genetic sequence data.

We have the Nagoya Protocol and there is a big discussion whether digital sequence information or genetic sequence data is included under that. And there are discussions going on in Geneva later in March to prepare for a big meeting later this year, the COP15, where that will be discussed specifically. The WHO is looking to BioHub system, which would be physical samples of pathogens, and there is an access and benefit sharing element to that. And then there's also discussions started on developing an international treaty on pandemics or an international instrument. And, again, there is an ABS element to that. And this causes concern because we want an unencumbered supply of pathogens as quickly as possible. And in order for us to achieve this 100 day mission that was discussed by the G7, the ABS legislation is not going to help with that if it causes delays in the sharing of pathogens.

So, in summary, I just wanted to spend the time on Nagoya so that people understand how serious this is, not just for influenza, but it particularly

impacts it because we change the vaccine every season. So, in summary, so the current Northern Hemisphere season, despite extremely low circulation of influenza viruses, the viruses continue to evolve. Which resulted in the vaccine composition being updated and there were two changes. The great news was that the CVV's and potency assay reagents were supplied within normal the timeframes, despite some of the challenges we were still facing due to COVID. We did have some issues with supply, materials, and components, and some issues with transport and freight, but in the end we were able to work around those. Approximately 174 million influenza vaccine doses were supplied to the U.S. market, but the vaccine uptake rates were slower and lower than the last two seasons.

Influenza is a serious and, yet, often underestimated disease for which vaccination is the best means of protection. So we certainly want to maintain and increase vaccination rates to provide protection against this disease. The Nagoya Protocol and ABS legislation is continuing to pose challenges

and increasing challenges, and it impacts our ability to select and manufacture the best vaccine strains. And as I just said, the complexity of that ABS landscape is increasing and we're worried about further delays, but also, a sort of slacking of obligations as well, which might cause even more delays. And flu vaccination continues to be of great importance as the flu circulation increases and international travel resumes.

And I just want to finish on the teamwork theme. Again, so teamwork is needed to get the influenza vaccine over the finish line. And that includes getting people vaccinated. So in the interest of public health, the focus on the COVID-19 vaccinations must not negatively impact other vaccinations, including influenza. Thank you for your attention. Thank you.

Q AND A SESSION

DR. HANA EL SAHLY: (Audio skip) pertaining a

significant uptick in influenza vaccine update in the fifth year of the pandemic. It went back, the average, I guess, after the first year, the second year of the pandemic. Is that a global phenomenon from your perspective, you know, from what you have seen?

DR. BEVERLY TAYLOR: A number of countries, a similar picture. And I think so much focus has been on COVID-19, and I don't want to get into all the reasons and everything, but there's talk of vaccine fatigue because everybody has had (audio skip). Some people think if they've had the COVID-19 vaccine, they no longer need to get the flu vaccine. The low flu circulation may have made some people think that they no longer need the vaccination rate. I think a lot is due to messaging as well. I have to say, I mean, I'm based in the U.K., the U.K. rates have not seen the same decline. But I think there was a real push for both vaccinations over the winter months, so the general picture, I think, is that flu vaccinations have reduced compared to last year, certainly.

DR. HANA EL SAHLY: Right, any of my committee

colleagues with questions? I see one hand raised, two hands raised. So, Dr. Annunziato and Dr. Chatterjee. Beginning with Dr. Annunziato.

DR. PAULA ANNUNZIATO: Thank you. So I wanted to thank Dr. Taylor for those very clear and comprehensive comments on what it takes in order to get flu vaccines, really lifesaving flu vaccines to the world each year. I also wanted to comment so that the public and this committee understands that the concerns around the Nagoya Protocol and its potential to be a barrier for future effective responses to pandemics, is actually a concern that I believe all vaccine manufacturers share. Even those that do not work in the influenza space. And I think is a concern for many people who are working in this area of health security and pandemic response. So I wanted to reiterate that.

And, then, I also would note, the question came up around the trends of the influenza vaccine uptake in the United States during this past season, that it's my understand, and perhaps Dr. Cohn actually could comment on this as well if she's available on the

line, that in the United States, in fact, a number of vaccines have seen a drop-off since the COVID pandemic, in vaccine uptake. So this is a concern, actually I think for our entire population in terms of vaccine preventable diseases and having good protection. And bringing that health benefit to the people of the United States. But thank you very much.

DR. BEVERLY TAYLOR: Thank you.

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

DR. ARCHANA CHATTERJEE: Yes, thank you very much, Dr. Taylor, for your presentation. I'm not certain whether you are able to answer this question or not, but the question did come to my mind and perhaps some of our FDA colleagues who are on the call could also weigh-in. And that is with regard to the newer platforms, particularly the mRNA-based platforms that are being developed for influenza vaccines, for other vaccines too, but specifically for influenza vaccines, and the combination vaccines of COVID-19 and influenza. Are there discussions among the vaccine manufacturers

about how those would be incorporated into the available vaccines or is that too early yet to have those discussions?

DR. BEVERLY TAYLOR: I think, as an industry group we certainly researched it. A number of our companies are looking at new -- can you hear me? I'm getting strange messages. Yeah. So we have proven technologies for influenza vaccine manufacturing, and I think the new technologies are extremely exciting, but they still need to be proven for influenza. So, for example, if we had the pandemic today, influenza pandemic, we would still be heavily reliant on the proven technologies that we have today. But we certainly have been thinking about the new technologies and how we involve some of the newer companies in discussions around influenza and also things like Nagoya Protocol. Because a lot of the new technologies, the actual production bit is different, but all the supporting things around it, like getting your license and things that could impact it like Nagoya Protocol, they will face the same challenges as

the existing technologies, so we don't want to lose an advantage or something new if it gets bogged down in the same issues. So we still need to address these other issues. Not just the manufacturing process itself. Did I answer your question?

DR. ARCHANA CHATTERJEE: Yes, you did. Thank you.

DR. HANA EL SAHLY: Thank you. (Audio skip).

MR. MICHAEL KAWCZYNSKI: All right, again, thank you all for that portion of today's meeting. And it is now time for our lunch break. We're going to take, looking at the time, about 45 minutes. We'll make it a little bit more than that, so that we're going to reconvene at 1:45, actually, no, we're going to reconvene at 1:30. So see you all back then. That'll be 1:30 Eastern Time. About 37 minutes.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Okay, welcome back from our lunch break and to the 171st Vaccines and Related Biological Products Advisory Committee Meeting on Influenza. Let's get started and I'm going to hand it back over to our chair, Dr. El Sahly, take it away.

DR. HANA EL SAHLY: Thank you, Michael. Our next section of the meeting is for the Open Public Hearing session. I want to welcome you all to the Open Public Hearing Session. Please note that both the Food and Drug Administration, and the public, believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee Meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing Speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationships that you may have with the sponsor, its product and if known, it's direct competitors. Samples of this financial information may

include sponsors payments of expenses in connection with your participation in this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. So I think we have one OPH speaker. Go ahead.

DR. PRABHAKARA ATREYA: This is Prabha Atreya, thank you, Dr. El Sahly. Before I begin calling the designated speaker, I would like to just add the following items from FDA. FDA encourages participation from all public stakeholders in the decision making process. Every Advisory Committee Meeting includes an Open Public Hearing session during which interested participants may present relevant information or views. Participants during their OPH session are not FDA employees or members of this committee.

FDA OPH speakers may represent a range of viewpoints. The statements during this Open Public

Hearing session reflect the viewpoints of the individual speakers or of their organization but are not meant to indicate agencies agreement with the statements made. So, with that guidance, I would like to call upon Ms. Sarah Barry, who is listed to speak at this OPH session. Thank you. Ms. Barry, you can go ahead now.

MS. SARAH BARRY: Hello, can you hear me?

DR. PRABHAKARA ATREYA: Yes, very much.

MS. SARAH BARRY: All right, thank you very much. And thank you sincerely members of the Vaccine and Related Biological Products Advisory Committee. My name is Sarah Barry and I'm the new director of research and media relations for the SAFE Communities Coalition and I have no financial conflicts of interest. I continue to be humbled by the detailed and transparent discussions that have been had today. My goal is to make sure that your work, the research, the surveillance, the analyses, are not hindered by poor public health legislation. Next slide, please.

The SAFE Communities Coalition builds

grassroots coalitions, advocates for legislation, and educates the public about our pro-science message. We partner with family foundations, individuals, and other donors to build as broad a pro-science community as possible in states across the country. Next slide, please. We want to help you communicate science-based recommendations to policy makers, such as those that have been discussed at the committee today. We have found significant evidence that anti-vaccination activists are working directly with state politicians to undermine anything to do with vaccination, and that undeniably will include any recommendations made by the committee.

To help put these anti-vax influence into perspective, I'll be sharing a few pieces of research that we are releasing as an interim report. Next slide, please. So, as you can see on this slide, and I will say out loud for anybody who is vision impaired, we have 22 out of 50 states with anti-vaccination groups, 9 out of 50 states with anti-vaccination 501c4s, that's a registered political lobbying group.

Five out of 50 states with anti-vaccination PAC's, 20 out of 50 states with active pages on Facebook, and 12 out of 50 states with more than one activist group. And as our analysis continues, again, this is an interim report, it would be wise to expect that these numbers will increase significantly.

We wanted to get a better idea of how many states, obviously, again, have these groups. And a biproduct of that research was both the reminder that Facebook has continued to be an integral platform for the anti-vaccination community, and, again, a stark realization that it was actually very common for states to have multiple groups, sometimes even going beyond three or four groups in an individual state. I am from Ohio, and I have done a lot of awareness about this in Ohio, and we have at least two groups in Ohio, and one of them is considering an anti-vaccination PAC. Next slide, please.

So anti-vax legislation before the pandemic, flu vaccines were the target. Laws that were written about flu vaccine mandates have almost near identical

language to recent legislation regarding COVID vaccine mandates. And they feel safe recycling these arguments because the specific influence anti-vaccination activists have had on state politics went largely unnoticed. Next slide, please. Anti-vaccine PACs, it's important to note that many of these groups will not refer to them, obviously, under the term of anti-vaccine. They're branded as medical freedom or health freedom.

This is very important to note because it's a distancing tactic. They understand that the public perception of anti-vaccination attitudes is not in their favor and they're taking advantage of that by branding them as something else. Over the past few election cycles we have found hundreds of thousands of dollars raised and spent for anti-vaccine political purposes. And we also have evidence, again, that more PACs are imminent because they feel emboldened at the current lack of opposition to their PACs. Next slide, please.

Dr. Beverly Taylor made an excellent relay

race analogy in her presentation concerning the distribution of influenza vaccines. The legislative topics that I've been talking about are just additional hurdles in that relay race analogy. And, again, my goal is simple, it's to make sure that you all, the scientific community, the evidence-based community, knows the full extent of those hurdles within the United States so that your work is not wasted. Even more so beyond just simple hurdles, wouldn't it just suck to get to the end of the finish line and see local politicians taking the baton out of your hand and pushing you down on the ground.

And that is what I see as a very likelihood happening if the influence of these anti-vaccination lobbying groups are not addressed and at least understood, even if you don't call them out, at least having an awareness of what they're operating and the full extent, that is what is crucial. And that is my presentation, and we welcome any questions at this time. Thank you. Hello?

DR. HANA EL SAHLY: Well, I don't see any

raised hands for questions.

DR. PRABHAKARA ATREYA: Right. We will not take any questions at this time and since she's the only pre-registered OPH speaker, I think that concludes the OPH session. And then, in the interest of time, we can move forward with the next time item on the part of the session today. Thank you, Ms. Barry.

COMMITTEE DISCUSSION, RECOMMENDATIONS, AND VOTE

DR. HANA EL SAHLY: Thank you, Prabha. So we will be voting shortly on the new vaccine for the upcoming season in the Northern Hemisphere. The data we saw today point to a season of low circulation for influenza virus in general. A little more than first year of the pandemic, nonetheless we had still very few data to go by. There's indications that potentially there is an uptick in late February, but that remains to be seen on how it will evolve and whether it will wind down soon. It was largely an H3N2 season for the U.S., with globally a mismatch between the Northern

Hemisphere flu strain selective H3N2, the ones circulating we heard that the VE estimate is somewhere that is in the 15 to 18 percent we saw. But it was very wide confidence interval, pointing to a range potentially in this estimate.

And we did not see data on the impact on the sheer outcomes of disease, which previous seasons are any indicators, usually that outcome -- the efficacy against that particular outcome would be a bit higher. So, two strains are projected to be , the H1N1 and the H3N2. We heard that the reagents are available for cell-based and egg-based products. And I don't see any particular concerns.

The only thing that comes to mind is the declining (audio skip) and the issue of the Yamagata, which I think is too early to make any determination. It's two years' worth (audio skip) and their impact on all viral (audio skip).

So I invite my committee members to raise their hands in Adobe and if you like to make a comment, ask a question to David Wentworth. I see three raised

hands, we begin with Dr. Hank Bernstein.

DR. HENRY BERNSTEIN: Yeah, thank you. I was wondering what (audio skip) virus. Dr. Wentworth, you've noted the response to the 5A.1 virus subclade for the 6B.1A in 6 to 35 month old's was quite suboptimal. I mean, it seemed quite poor. Would this suggest the need for us to consider a change in the H1N1 vaccine strain?

DR. DAVID WENTWORTH: Yeah, I appreciate that question, and that's partly why I showed that data. With the pediatric population, H1N1 can be severe and so, it's a very important population to cover. The issue is two-fold. One, it's quite uncertain whether it's going to be a 5A.2 or a 5A.1 influenza season coming forward in the H1N1 season. So, for example, in 2022 and 2023, it could be a bit of a mixture. It could be 5A.1 most likely with that 155 substitute, which would be further advanced. Because the old 5A.1s, they've really been around since before we changed the vaccine to a 5A.2, so the preponderance of them in the United States community I think is going to

be quite low.

And that's partly why the 5A.2 vaccine was selected because we know it cross-protects against the 5A.1. Now, if you protect all of the adults, and the older pediatrics, say 3 to 17, actually that middle range in pediatrics, because they were around in the 2009 pandemic, have the least burden and the highest titer. So if they get vaccinated, they have a very low likelihood of transmitting it to, say, a younger sibling that may be in that very early window of age. And, so, all of those considerations were made in the BCM process at the WHO meeting, and so really we have one cohort in that age range that's the most susceptible to this other strain.

But they would also be the most susceptible to 5A.2s, which are more likely to predominate. They have more an antigenic advance coming out of India, so those additional ones, like I showed you that India Punay (phonetic) used in our serology studies, that is the most antigenically advanced 5A.2 virus. It's the most antigenically advanced H1 virus. And, so, when you

consider our population as a whole in the United States in particular, we've seen quite a bit of the 5A.1s prior to the pandemic. And vaccinated against the 5A.1s, and our first vaccination against 5A.2s occurred in this particular season, the 2021-'22 season. And the big recommendation was to not go forward into a more advanced 5A.2 vaccine virus, because that didn't appear warranted based on the serology studies and the antigenicity studies.

And, so, really it's a matter of that very small sliver of our population versus the entire population. And by protecting the entire population, we may protect that small sliver. What we would communicate very heavily, both through the ACIP and through position networks, *et cetera* was if we started to see a 5A.1 season, this would be something we would communicate that treatment is advisable for that very, pediatric population. Test early, treat early. And, so, that's the logic behind the recommendation. I hope that addresses it.

DR. HENRY BERNSTEIN: Yes, thank you.

DR. HANA EL SAHLY: Dr. Offit?

DR. PAUL OFFIT: Right, thank you. So, David, I have a question that's sort of a follow up to Hana's earlier question. Regarding the importance of neuraminidase, and considering neuraminidase, we make these decisions. We now have a fair amount of experience with FluBlok, which only contains the hemagglutinin. Has that educated to any extent about the importance of paying attention to neuraminidases as we're creating these strands?

DR. DAVID WENTWORTH: Yeah, so far it really hasn't educated us that much about it. And I would tell you there's a couple of reasons we need to think about that from a group like this, that you need to think about it, and contribute your ideas to even the regulatory community. One, the FluBlok uses 45 micrograms of antigen, so it's uses three times more antigen than an egg-based or cell-based vaccine. So that's one difference. And then it doesn't have NA. We don't have, as far as I'm aware, there are not platform specific VE studies that have been completed

yet. In part because of the pure market share of the different vaccines (audio skip) are much lower prevalent, like the cell-based now is getting up to 30-40 million doses.

And I don't know off the top of my head what FluBlok is. But that is something that I think is needed either, maybe even in RCTs or some other type of study. You know, test-negative design won't capture something like FluBlok difference from cell-based or egg-based.

The other thing I would say is that comparison may be difficult because we do not require a specific quantity of NA in the vaccines that could have NA. So we're relying solely on co-purification of the NA in a process (audio skip). The thing that is tracked in the purification process is the hemagglutinin.

So if you're a vaccine manufacturer, are you going to change a process because you're reducing the NA that's co-purifying it, or are you only going to change a process if your HA is going down or up, right? So I think some of the incentives that a manufacturer

may have are purely on the HA and the NA is there by happenstance. And if you just, at the very first purification step of an influenza virus particle, generally, this is a little bit of a generality, but they'll be one quarter the NA as HA because there's about 100 neuraminidase molecules on the surface of a particle and 4 to 600 hemagglutinins.

And, so, just by doing that stoichiometry, you're always going to have, so a quarter of the amount of NA antigen in the, and then you're depending on co-purification of that. And, so some of this may come to light with new vaccines as well, Dr. Offit. If people using recombinant approaches or DNA, RNA approaches decide to start putting those in at equal molar levels, I think they could be a big benefit. It could be a big benefit to mitigate drift in the, we see drift in both the HA and NA, so clearly the NAs the target of our immune system, and clearly the NA antibodies won't protect us from infection, but they will protect from dissemination of the infection. So they block, it acts just like a neuraminidase inhibitor blocking the

activity of that enzyme.

And they, of course, can do antibody-dependent cellular cytotoxicity, CTLs, all of that. And, so, it's a long-winded answer that says I don't know, so I apologize for that. But I am thinking along the lines I think of many in this committee where we would like to see NA be more of a part of a holistic flu vaccine. But we don't know from FluBlok yet if it's told us anything.

DR. PAUL OFFIT: Thanks, David.

DR. HANA EL SAHLY: We have two additional raised hands. Beginning with Dr. Berger.

DR. ADAM BERGER: Hi. Thanks very much and this should just be a pretty quick, clarifying question. I just wanted to ask about the Yamagata strains that were detected, or reported, I guess. You had mentioned in your talk that there were 13 and Commander Gustin had reported that they had actually identified one. I just wanted to make sure there wasn't overlap there. The one from DoD is not included in the 13 that you had actually screened, correct?

DR. DAVID WENTWORTH: Well, I actually don't know. I was going to circle back with him, maybe he's on and he knows whether or not they investigated that further. Like I said, there's a big iceberg and we want to track down any that are potentials. One that I know of that was tracked down by the collaborating center in Crick, had the exact same sequence as a live attenuated vaccine B/Phuket/HA, so that one we're pretty confident was a false Yamagata identification by PCR.

DR. ADAM BERGER: Thanks, that's where I was trying to get an understanding. It's just the detection problem or --

DR. DAVID WENTWORTH: Yeah, I'm sorry I don't have a better answer. I will circle back and see if that's in the 13 or if it's a 14th that maybe we want to investigate further.

DR. ADAM BERGER: Thank you.

DR. HANA EL SAHLY: And Dr. Monto.

DR. ARNOLD MONTO: Thank you.

DR. DAVID WENTWORTH: The Emeritus Professor

now.

DR. ARNOLD MONTO: Hello. Yes. But still working on VE studies.

DR. DAVID WENTWORTH: Yeah.

DR. ARNOLD MONTO: I want to commend you for all the work you are doing with strain selection. And acknowledge the frustration we all feel about next years, we had a question about the choice of the H1N1, I remember, in 2019. 2020, we had H1N1 viruses that some of them were susceptible to the vaccine, protected by the vaccine, and some were not. Also, I've been reviewing the Southern Hemisphere recommendations and the subsequent Northern Hemisphere recommendations and it's very clear that five years out of the last ten, I believe, the correction of the Northern Hemisphere recommendation by later evidence was put into the Southern Hemisphere vaccine recommendation.

Which then became the Northern Hemisphere recommendation for the next year. And this is sort of trying to catch up when you can't catch up in the process. And I just want to make an appeal that after

we've been busy with COVID for the last couple of years, we not forget the universal influenza vaccine programs which were started to try to get us out of this situation, which a new terminology, which I prefer, is super seasonal.

We need super seasonal vaccines so that we don't live with this kind of catching your tail situation, which I think is inevitable no matter how careful you go through the strain selections. So just a comment and appreciating your frustration with this, and in test negative studies and all the rest, so thank you.

DR. DAVID WENTWORTH: Thank you very much, Dr. Monto, what I've done pales in comparison to what you've done and so, I'm continually impressed by all the studies and all of the work in Michigan. It's such a tremendous team of investigators there. I do also -- chronically, I share your frustration with not having the data in time to, so, for example, the Southern Hemisphere recommendation, (audio skip) vaccine virus was isolated about a couple weeks after our meeting

here. And then, of course, it takes about three months to develop it as a vaccine virus, right? So first you have to isolate it, then you have to do the analysis with (inaudible) and things like that to understand it's a good antigen.

And then you have to get it into the reassortant labs and do the analysis of those vaccine viruses and their gross properties in cell-based vaccines and in egg-based vaccines. Really before it can be nominated as a vaccine, and the baton, you have to hand the baton to a manufacturer. You can't say, this is the one we would like, right? All of us share that frustration. And I think the other thing that's underappreciated that I tried to do in this particular presentation, was to show and mitigate the drift. And H3N2 is the fastest drifting virus. Other things we can do to mitigate the drift, we just talked about neuraminidase. Another thing, I am very involved in the COVID response and the COVID vaccines, and what you may not appreciate in whole sets of data, is the titers for a COVID vaccine are (audio skip) they're not in the

hundreds. So the neutralizing titers are in the thousands.

We could go a long ways to mitigate drift by having higher titer produced from our vaccine. And so that's a, it's a little bit different, I've been trying to always get in front of antigenic evolution, which at any moment in time is a snapshot, right? We can take a picture right now and I can tell you right now (audio skip) that I'm worried about that one went to 192, you know, the 53N and the 53G, the Maryland-like one. And what we already (audio skip) 1A, they could easily have emerged in the 2a2 vaccine, like if we went on with a Bangladesh vaccine, which would have been the only choice at the time, then that would have only protected against (audio skip) not against Cambodia-like viruses, which occur now and then, and not against the other clades.

So, I don't know, you gave me an opportunity to talk to you about it, but I wish we made decisions every couple of months, and we'd probably be in a little bit better shape. He does a fantastic job

looking at all the data, being critical, and I do think one thing that's really underappreciated is stepping forward does improve our VE. It's just hard to see. And I can clearly see it with the immune, the serum. That's a more direct measure.

DR. ARNOLD MONTO: Thank you.

DR. HANA EL SAHLY: I do not see any more questions or comments from the committee judging by no raised hands. With that we probably need to move to voting part of the meeting. Dr. Atreya?

DR. PRABHAKARA ATREYA: Yes, thank you. Dr. El Sahly. The voting will be done, I think we're going to be projecting the voting questions and then there will be one voting question from that, and then we will vote on each question separately. And Christina Vert, Michael therefore will be conducting the voting process, she'll have some instructions then followed by the voting. So, Christina, you want to start and Mike, do you want to present the voting questions on the screen please?

MR. MICHAEL KAWCZYNSKI: Okay.

MS. CHRISTINA VERT: Thank you. I will go ahead and describe the voting process. Only our members and temporary voting members will be voting at today's meeting. With regards to the voting process, Dr. El Sahly will read the final questions for the record and afterwards, all members and temporary voting members will cast their vote by selecting one of the voting options, which include yes, no, or abstain. You will have two minutes to cast your vote after the question is read.

And please note that once you have cast your vote you may change your vote within the two minute timeframe, however, once the poll has closed all votes will be considered final. Once all the votes have been placed, we will broadcast the results and read the individual votes aloud for the record. And does anyone have any questions before we begin? Okay, I don't see any questions. Okay, Dr. El Sahly, if you could please read the voting question?

DR. HANA EL SAHLY: Question one: For the influenza A (H1N1) component of the 2022-2023 influenza

virus vaccines in the U.S., does the committee recommend: A/Victoria/2570/2019 (H1N1) pandemic 09-like virus for the egg-based vaccines; A/Wisconsin/588/2019 (H1N1) pm09-kuje virus (Cell- or recombinant-based vaccines)?

MS. CHRISTINA VERT: Okay, at this time, you may vote, and we'll start the timer at two minutes.

MR. MICHAEL KAWCZYNSKI: Just a reminder to voting members that at the bottom of your screen, dead center, you will see the voting question. Again, you have the option of yes, no, or abstain. There is no submit button, just pick whichever you prefer. We have about one more minute for you to make your selection.

MS. CHRISTINA VERT: Okay, it looks like all the votes are in. And at this time the two minutes are up. And, so, Michael if you could please end the vote by closing the poll? Okay. Okay, there are 11 total voting members for this particular vote, the vote is unanimous, 11 out of 11 votes.

DR. PRABHAKARA ATREYA: Mike, do you want to broadcast the results please?

MR. MICHAEL KAWCZYNSKI: The votes are broadcast.

DR. PRABHAKARA ATREYA: Okay, thank you.

MR. MICHAEL KAWCZYNSKI: You have to read the names if you'd like.

MS. CHRISTINA VERT: Yes, I'm going to go ahead and now read the names. Dr. Berger, yes. Dr. Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes. Dr. James, yes. Dr. Portnoy, yes. Dr. Offit, yes. Okay, so I am done with that vote, and I will pass this back over to Dr. El Sahly.

DR. HANA EL SAHLY: Question two: For the influenza A (H3N2) component of the 2022-2023 influenza virus vaccine in the U.S., does the committee recommend an A/Darwin/9/2021 (H3N2)-like virus for the egg-based vaccines; an A/Darwin/6/2021 (H3N2)-like virus (cell- or recombinant-based vaccines)? Vote yes, no, abstain.

MS. CHRISTINA VERT: Thank you. Go ahead and vote. We start the two minutes, again, at this point. All right. The voting's almost done. Looks like all

the votes are in. We can go ahead and end the poll. Okay. Again, we have a unanimous vote, 11 out of 11 voting yes. And I will go ahead and read the votes. Okay. All right I'm going to go ahead, oh, wait a minute. Give me a minute. Okay. Michael, did you end the poll? Poll closed, okay. I'll go ahead and read the votes. Dr. Berger, yes. Dr. Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes. Dr. James, yes, and Dr. Portnoy, yes. Dr. Offit, yes. And that concludes my reading of the results for the second vote. I will hand it back over to Dr. El Sahly.

DR. HANA EL SAHLY: Question three: For the influenza B component of the 2022-2023 trivalent and quadrivalent influenza virus vaccines in the U.S., does the committee recommend inclusion of a B/Austria/1359417/2021-like virus for B/Victoria lineage? Vote please yes, no, or abstain.

MS. CHRISTINA VERT: Okay, at this time you can start the two minute timer and you can start voting. Thirty seconds left. Okay. Looks like all

the votes are in. At this time, the two minutes are up. And I want to say that we had one additional voting member join us now, so we do have 12 voting members for this particular vote at this time. We have a unanimous vote, 12 out of 12. And I will read the votes for the record. Dr. Cohn, yes. Dr. Berger, yes. Dr. Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes. Dr. James, yes. Dr. Portnoy, yes, and Dr. Offit, yes. That concludes my reading of this vote, and I will pass this now to Dr. El Sahly.

DR. HANA EL SAHLY: Question four: For the quadrivalent 2022-2023 influenza vaccine in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus for the Yamagata lineage as the 2nd influenza B strain in the vaccine? Yes, no, or abstain.

MS. CHRISTINA VERT: At this time, you may start voting and the timer has started for two minutes. You have 30 more seconds for the vote. It looks like all the votes are in, so we will close the vote. We

have a unanimous vote, 12 out of 12 voting yes. And I will read the specific votes for the record. Dr. Cohn, yes. Dr. Berger, yes. Dr. Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes. Dr. James, yes. Dr. Portnoy, yes. And Dr. Offit, yes. That concludes my reading of the votes and the voting portion for today's meeting. I will now hand the meeting back over to Dr. El Sahly.

DR. HANA EL SAHLY: Thank you, Christina. Do you mind putting the names of the voting members on the screen again? So now we will go the round table, virtual round table to ask the members for their rationale of their vote. I will begin with myself. Dr. Wentworth presented data pertaining to the risk of the virus, the H1N1, the H3N2. That is convincing that those two strains might circulate and remain among this population, the six (audio skip) stage should the 5A.1 rear its head would they be (audio skip) or not. The treatment approach of course is important, but also giving them their first two doses because partial

immunity is expected to prevent some severe outcomes, at least in a fraction. Should that be the case, so this was my rationale for voting yes. Dr. Monto? Cannot hear you.

DR. ARNOLD MONTO: Yep. I think that this is the best of the possible outcomes right now. We have a good, not a great, vaccine. And we try to make it better by being very careful in strain selection. I join some of my colleagues in wondering about the replacement of the B/Yamagata with another H3N2 to hedge our bets, among other things. And to get us higher titers as Dr. Wentworth mentioned. So I think we go with the experts who have spent a long time working on this and we can't do any better. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Monto. Dr. Berger.

DR. ADAM BERGER: Thanks very much for a well-run meeting, by the way. And just want to say, I agree with everything you both said already. I think the evidence around the strains are currently prevalent. They're expected to be here in the U.S. in this next

flu season, plus the reactivity rates for each one of the vaccines that were being, or for each of the viruses and the ability to (inaudible) against that suggest that these are really the best strains we ought to put in. I do also reflect the same question around the B/Yamagata lineage and whether it's necessary at this point. But I think without further understanding if it really is (inaudible) or if it's not, it's probably the best idea to include it still at this point. Something for the committee to take up at a later date though.

DR. HANA EL SAHLY: Thank you, Dr. Berger. Dr. Cohn. You are muted.

DR. AMANDA COHN: Can you hear me? Sorry. First of all, I apologize for missing part of the meeting, I had an unexpected issue. But I don't have anything more to add than the prior members. I think that in the current setting, this remains the best choice, at least for this year. And I know that my CDC colleagues will continue to watch this very closely.

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

DR. ANDREA SHANE: Thank you very much for the really helpful and very informative presentations. I agree with everything that has been said before. I think we've had a blessing and a curse in not having a very robust influenza season and based on the information that we have, this helped to inform my decision. I also would love to have as much information as we can on the younger population because this is one of interest, and I think one that often has the most severe consequences from influenza infection, so thank you very much.

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

DR. ARCHANA CHATTERJEE: Yes, my vote was based on the data presented by colleagues from the CDC and the DoD. As some of the members of the committee have already said, these are the best data we have based upon which to make our decision today. And, so, I voted based on that information. Thank you.

DR. HANA EL SAHLY: Thank you, Dr. Chatterjee. Dr. Kim?

DR. DAVID KIM: Oh, thank you so much, everyone, who made the time and the effort to make the presentations today. And I don't have much to add, other than what's been said already, other than this actually would make our recommendation for, when people ask health care providers whether they should get the quadrivalent versus trivalent vaccine. Because of all that's been said about the B/Yamagata version.

And, actually, given the discussion we had with some nuances on the composition of the flu vaccine, it really does call for, so that we all can be in a more comfortable place when making these decisions of the need and the urgency to develop a universal vaccine. So, with that, I just want to say thanks to our colleagues who presented all the information and also, that our recommendation is consistent with the WHO recommendation and that they mutually validate one another. So, thanks to all those people who made tireless work to make these decisions as easy as possible.

DR. HANA EL SAHLY: Thank you, Dr. Kim. Dr.

Bernstein?

DR. HENRY BERNSTEIN: I appreciate the comments that everyone made and agree with what the U.S. and the global surveillance data suggests, and I was satisfied with Dr. Wentworth's incredibly detailed presentation and explanation regarding whether or not to consider changing the H1N1 strain, because I do worry about those younger pediatric patients. And I think that all the wonderful work that's done by the CDC and others will keep us informed if changes need to be made. Thanks to everyone.

DR. HANA EL SAHLY: Dr. Janes?

DR. HOLLY JANES: Thank you, nothing much to add. I agree with all the statements that have been made previously and I want to thank the speakers for really incredibly thoughtful presentation. These presentations seem to get more complex each year, but even more nuanced and I really appreciated the work that went into helping us think through the difficult choices that need to be made, and the need for making a decision now in order to make the production and

distribution timeline. I do want to second my suggestion from earlier to perhaps consider revisiting the data from a given year when we look at the data for next year to see how well the final VE estimates map alongside the immunology and the phylogenetic data that we've been presented. But thank you very much.

DR. HANA EL SAHLY: Thank you, Dr. Janes. Dr. Portnoy?

DR. JAY PORTNOY: Yeah, again, I'd like to thank the speakers for their presentations. I'm really impressed by the surveillance system, it's really detailed and pretty amazing. I continue to be concerned about the fact that what we're basically doing is a guessing game. We're playing a game of whack-a-mole where we develop the vaccine, whatever vaccine we develop will put pressure on the virus to mutate into something else, so we're never going to be able to catch up with it.

And it's something that we have to take into consideration. I would strongly urge that the industry that produces the vaccines consider ways of either

increasing the number of strains that can be included or using technology such as mRNA to increase the titers so that you have a broader effectiveness of the vaccines. Because until we do that we're really just kind of chasing our tails. Virus will always find a way. But this is the best we can do right now and I'm happy with it. Thank you.

DR. HANA EL SAHLY: An interesting hypothesis to test. Dr. Offit?

DR. PAUL OFFIT: Yes, I'd like to thank our speakers for making a very difficult subject much easier to understand. I mean, this is one elusive virus. I trained in a flu lab in the early 1980s at The Wistar Institute, in Walter Gerhard's lab, and he was using monoclonal antibodies to define structure functional relationships with the virus, and he was working on a universal flu vaccine, I mean, he used matrix protein to try and make a universal flu vaccine. This was 40 years ago, I mean, it tells you how hard it is to do that. And I suspect Dr. Portnoy eludes to that we're probably going to be dealing with this on a

yearly basis for a while. But thanks, and again, thanks to the speakers.

DR. HANA EL SAHLY: Thank you. And last, but not least, Dr. Badzik.

DR. DOUGLAS BADZIK: First off, I wanted to just thank everybody for the opportunity to participate in this whole entire discussion. And for the presentations. I thought that they were incredibly well-presented in breaking down some very complex subjects into a way that was very understandable. My reason for voting was I just saw no compelling reason to go and deviate from what the World Health Organization had recommended. In particular in the season when we did have a kind of limited ability to have samples and surveillance compared to previous seasons.

I think, particularly, the discussion that I found incredibly useful was the discussion surrounding H1N1 and kind of the discussion with regards to the younger populations, and I think that will be something that will be very important for us to follow through

this upcoming flu season, is to ascertain was that the right decision, which it seems like it is. But, once again, thanks everybody, and that's all I have.

DR. HANA EL SAHLY: I think we heard from all of our members regarding the rationale of their vote. And, with that, I turn the meeting over to Dr. Atreya.

DR. PRABHAKARA ATREYA: Thank you, Dr. El Sahly, thank you all the members and the speakers. And then, with that, I think the meeting is formally adjourned now, 2:29. Thank you so much and have a good afternoon. Bye-bye.

DR. HANA EL SAHLY: Bye.

[MEETING ADJOURNED FOR THE DAY]