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Center for Biologics Evaluation and Research (CBER)
177th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Web-Conference
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October 6, 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.

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NO PUBLIC COMMENTERS	

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OPENING REMARKS: CALL TO ORDER

MR. DEREK BONNER: Good morning, everyone. Today's date is October 6, 2022. My name is Derek Bonner. I'm a member of the AV support team for these proceedings, and I'd like to formally welcome you to the 177th meeting of the Vaccines and Related Biological Products Advisory Committee.

At this time, I'd like to hand the meeting over to our Chair, Dr. Hana El Sahly.

DR. HANA EL SAHLY: Good morning, everyone. I welcome the members, the participants, and the public to the 177th Meeting of the Vaccines and Related Biological Products Advisory Committee. The topic today will be strain selection for the Influenza virus Vaccine for the 2023 Southern hemisphere Influenza season.

We will begin our meeting today with some administrative announcement, roll call, and Conflict of Interest Statement by the designated federal officer of the meeting, Dr. Sussan Paydar.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, CONFLICT OF INTEREST STATEMENT

DR. SUSSAN PAYDAR: Thank you, Dr. El Sahly. Good morning, everyone. This is Dr. Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer, DFO, for today's 177th Vaccines and Related Biologic Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone for today's virtual meeting.

Today, the Committee will meet in open session to discuss the strain selection for the influenza virus vaccines for the 2023 Southern hemisphere influenza season. Today's meeting and the topics are announced in the Federal Register Notice that was published on August 18, 2022. At this time, I would like to introduce and acknowledge outstanding leadership of my division director, Dr. Prabhakara Atreya, and the excellent work of my team, whose contributions have

been critical for preparing today's meeting.

Christina Vert is my backup DFO and will be supporting me throughout the meeting today. In addition to Christina, other staff who contributed significantly and provided excellent administrative support are Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lashawn Marks. I also would like to express our sincere appreciation to Mr. Derek Bonner in facilitating the meeting today.

Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes, trying to ensure that today's virtual meeting will also be a successful one, like all the previous VRBPAC meetings. Please direct any press media questions for today's meeting to FDA's Office of the Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles. We will begin today's meeting by taking a formal roll call for the Committee members and the temporary non-voting member.

When it is your turn, please turn on your video camera, unmute your phone, and then state your

name and last name. And, when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides, in which we'll begin with the Chair, Dr. Hana El Sahly. Hana.

DR. HANA EL SAHLY: Good morning, everyone. Hana El Sahly, Baylor College of Medicine. I am an adult infectious diseases physician, and my research focuses on clinical vaccine development.

DR. SUSSAN PAYDAR: Thank you. Dr. Hayley Altman-Gans.

DR. HAYLEY ALTMAN-GANS: Good morning, everybody. My name is Dr. Gans, Hayley Gans, and I'm pediatric infectious disease at Stanford. My research focuses on the immunology, the host pathogen interface, and with particular interest in vaccine responses. Thank you.

DR. SUSSAN PAYDAR: Great. Thank you. Dr. Paula Annunziato, non-voting member, our industry representative. Paula.

DR. PAULA ANNUNZIATO: Good morning, everybody. Waiting for my video to come up. Good

morning, everybody. My name is Paula Annunziato. I am the head of Vaccine Clinical Research at Merck, and I am today's non-voting industry representative.

DR. SUSSAN PAYDAR: Great. Thank you, Paula. Dr. Adam Berger.

DR. ADAM BERGER: Just waiting for the video to pop in.

DR. SUSSAN PAYDAR: Yes.

DR. ADAM BERGER: Okay. Hi, Adam Berger. I'm the Director of the Division of Clinical and Healthcare Research Policy here at NIH.

DR. SUSSAN PAYDAR: Great. Thank you. Dr. Henry Bernstein. Hank.

DR. HENRY BERNSTEIN: Good morning, everyone. My name's Hank Bernstein. I'm a professor of pediatrics at the Zucker School of Medicine at Hofstra/Northwell. I'm a general pediatrician with expertise in vaccines. Thank you.

DR. SUSSAN PAYDAR: Thank you. Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: Ah, here's my video.

Good morning, everyone. My name is Archana Chatterjee. I have the privilege to serve as dean of Chicago Medical School and Vice President for Medical Affairs at Rosalind Franklin University of Medicine and Science in North Chicago. I'm a pediatric infectious diseases specialist with a focus in the field of vaccines.

DR. SUSSAN PAYDAR: Thank you, Archana. Captain Amanda Cohn.

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

DR. SUSSAN PAYDAR: Thank you, Amanda. Dr. Holly Janes.

DR. HOLLY JANES: Good morning. I am Holly Janes. I am a professor at the Fred Hutch Cancer Center in Seattle, a biostatistician by training, and my specialty is vaccine evaluation.

DR. SUSSAN PAYDAR: Great. Dr. Arnold Monto.

DR. ARNOLD MONTO: Good morning, I'm Arnold Monto. I'm at the University of Michigan School of

Public health, where I've worked on epidemiology and prevention mainly of respiratory infections, particularly influenza.

DR. SUSSAN PAYDAR: Thank you. Dr. Paul Offit.

DR. PAUL OFFIT: Good morning, I'm Paul Offit. I'm a pediatric infectious disease specialist at Children's Hospital Philadelphia and the University of Pennsylvania School of Medicine. My interest is in vaccines, specifically mucosal vaccinees. Thank you.

DR. SUSSAN PAYDAR: Thank you. Dr. Steven Pergam.

DR. STEVEN PERGAM: Hi, everyone. I'm Steve Pergam. I'm a professor in the Division of Vaccine and Infectious Diseases at Fred Hutchinson Cancer Center. My particular focus is on infections in immunocompromised patients.

DR. SUSSAN PAYDAR: All right. Thank you. Dr. Stanley Perlman.

DR. STANLEY PERLMAN: Good morning. I am Stanley Perlman in the Department of Microbiology and

Immunology and Pediatrics at the University of Iowa, and my specialty is pediatric infectious diseases and Coronaviruses.

DR. SUSSAN PAYDAR: Great. Thank you, Stanley. Dr. Jay Portnoy, our consumer representative.

DR. JAY PORTNOY: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri, Kansas City School of Medicine. I'm also an allergist, immunologist in the Division of Allergy, Immunology at Children's Mercy Hospital in Kansas City.

DR. SUSSAN PAYDAR: Thank you, Jay. Dr. Eric Rubin.

DR. ERIC RUBIN: Good morning, I'm Eric Rubin. I'm at Harvard, the Brigham and Women's Hospital, and at the New England Journal of Medicine.

DR. SUSSAN PAYDAR: Thank you, Eric. Dr. Andrea Shane.

DR. ANDREA SHANE: Good morning, I'm Andy Shane. I'm a professor of pediatric infectious diseases at Emory University and Children's Healthcare

of Atlanta. My area of interest is in vaccines and vaccine response, especially related to enteric infections. Thank you.

DR. SUSSAN PAYDAR: Thank you, Andy. Next, we will do a roll call for our temporary non-voting member, Dr. David Wentworth. David.

DR. DAVID WENTWORTH: Good morning, my name is David Wentworth. I'm the chief of the Virology Surveillance and Diagnostics Branch in the Influenza Division, and I'm also the U.S. National Influenza Center Director and the director of our WHO Collaborating Center for Influenza, Surveillance, Epidemiology, and Control. Good morning.

DR. SUSSAN PAYDAR: Thank you, David. Good morning. Great. Thanks everyone. We have a total of 15 participants, 14 voting and one non-voting member. Now, I'll proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, October 6, 2022, for the 177th Meeting of the Vaccines and Related Biological

Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as the chair for today's meeting.

Today on October 6, 2022, the Committee will meet in open session to discuss the strain selection for the influenza virus vaccines for the 2023 Southern Hemisphere influenza season. This topic is determined to be a particular matter involving specific parties, PMISP.

With the exception of the industry representative member, all standing and temporary voting or temporary non-voting members of the VRBPAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subject to Federal Conflict of Interest laws and regulations.

The following information on the status of this Committee's compliance with Federal Ethics and Conflict of Interest law, including but not limited to 18 U.S.C. Section 208, is being provided to

participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGE and SGE consultants, of this Committee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary non-voting members, are in compliance with federal Ethics and Conflict of Interest laws.

Under 18 U.S.C. Section 208, Congress has authorized 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 a conflict of interest created by the financial interest involved or when the interest of the regular government employee 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 Conflict of Interest waivers have been issued under 18 U.S. Code 208 in connection with this meeting. We have the following consultants serving as a temporary non-voting member and speaker for this meeting, Dr. David Wentworth.

Dr. David Wentworth, is the Director of WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, and he's employed by the Centers for Disease Control and Prevention as Chief of the Virology Surveillance and Diagnosis Branch in the Influenza Division. He is an internationally known expert in influenza virus epidemiology, worldwide

influenza disease burden, and influenza vaccines.

Dr. Wentworth is a regular government employee and has been screened for conflicts of interest and cleared to participate as both a speaker and as a temporary non-voting member for today's meeting. Disclosure of conflicts of interest for speakers follows applicable federal laws, regulations, and FDA guidance.

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 authorized to participate in the Committee discussions in general. However, he is not authorized to participate in the Committee voting process. Dr. Paula Annunziato of Merck will serve as the industry representative to this Committee. Industry representatives are not appointed as a special government employee and serve as non-voting members of the Committee.

Industry representatives act on behalf of all related industry and bring general industry perspective

to the Committee. Industry representatives on this Committee are not screened, 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 as special government employees and are screened and cleared prior to their participation in the meeting.

They are voting members of the Committee. FDA encourages all meeting participants, including 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 members, consultants, and participants that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time I would like to hand over the meeting to Dr. El Sahly. Thank you.

INFLUENZA VIRUS VACCINE STRAIN SELECTION - 2023 SOUTHERN HEMISPHERE

DR. HANA EL SAHLY: Thank you, Sussan. We will kick off the meeting with Dr. Jerry Weir. Dr. Jerry Weir, Director of the Division of Viral Products, Office of Vaccines Research and Review, CBER/FDA. Dr. Weir will go over influenza virus vaccine strains selection 2023 Southern Hemisphere. Dr. Weir.

DR. JERRY WEIR: Thank you, Hana. Good morning, everyone, and welcome. I'm going to just give a very brief introduction to the topic today essentially to remind everybody why we're here. I think you guys are going to move my slides for me, so you can go ahead to the second slide. Okay. So the purpose of today's VRBPAC Committee meeting discussion

is to make recommendations for the strains of influenza A, H1N1 and H3N2, and B viruses to be included in the 2023 Southern Hemisphere formulation of influenza vaccine licensed in the United States.

But why do we do this? Since 2016, some U.S. manufacturers, actually two to be specific, have been approved to produce a Southern Hemisphere formulation for their influenza vaccine. Both of these manufacturers are egg-based vaccines. We follow the same strain recommendation and supplement approval process for these manufacturers in these Southern Hemisphere formulations as we do for the Northern Hemisphere process, which usually, as everyone knows, takes place in February or March for the following year.

It's essentially the same procedure. Go to the next slide. Okay. And this is the somewhat-abbreviated presentation compared to what we do for the Northern Hemisphere because, as I said, there's only a couple of manufacturers involved, and it only applies to the Southern Hemisphere formulation. But you see

the same type of data. You'll get a review of the epidemiology of circulating strands and surveillance data from the U.S. and from around the world, and this is summarized from a recent WHO Southern Hemisphere strain selection consolation.

During that talk, you will hear about antigenic relationships among contemporary viruses and candidate vaccine strains that are available. A lot of the data will be hemagglutination inhibition and virus neutralization test data using post-infection ferret sera, HI, and virus neutralization tests using panels of sera from humans receiving recent inactivated influenza vaccines. You'll probably be presented some antigenic cartography as well as phylogenetic analyses of HA and NA genes. Next slide.

About a year ago, this Committee met and made a recommendation for the Southern Hemisphere influenza vaccines for 2022, in other words the influenza season that's pretty much concluded in the Southern Hemisphere now. The WHO made a recommendation the 24th of September 2021, and they recommended the following

viruses be used for egg-based trivalent influenza vaccines in the Southern Hemisphere 2022 season: an A/Victoria/2570/2019 H1N1 pandemic-like virus, an A/Darwin/9/2021 H3N2-like virus, and a B/Austria/1359417/2021-like virus of the B/Victoria lineage.

They also recommended that any quadrivalent vaccines containing two influenza B strains contain those three strains plus a B/Phuket/3073/2013-like virus in the B/Yamagata lineage. Our VRBPAC met on September 30th following that recommendation and made the same recommendation for the U.S. manufacturers of Southern Hemisphere formulation. Next slide.

More recently, when we met in March, we did the recommendation for the Northern Hemisphere vaccines, in other words, the vaccine that are being rolled out about now for use in the United States and other Norther Hemisphere countries. At that time, February 25th, the WHO made a recommendation, and they recommended for egg-based vaccines for following viruses be used for trivalent influenza vaccines for

the 2022-2023 Northern Hemisphere season.

Once again, it was actually the same set of viruses that were recommended previously for the Southern Hemisphere in 2022, an A/Victoria/2570/2019 H1N1 pandemic-like virus, an A/Darwin/9/2021 H3N2-like virus, and a B/Austria/1359417/2021-like virus from the B/Victoria lineage. Again, they recommend that a B/Yamagata strain be included in quadrivalent vaccines, and this was the B/Phuket/3073/2013. Our VRBPAC met, reviewed the data, and made the same recommendation on March 3, 2022. Next slide.

Okay. So, more recently, two weeks ago, the WHO met and made a recommendation for the upcoming Southern Hemisphere season. This was on September 23rd. There was one change from the previous recommendations, and you'll see they recommended an A/Sydney/5/2021 H1N1 pandemic 09-like virus in addition to the previously recommended A/Darwin/9/2021 H3N2-like virus and a B/Austria/1359417/2021-like virus from the B/Victoria lineage.

The fourth strain recommended for quadrivalent

vaccines remained the B/Phuket/3073/2013-like virus from the B/Yamagata lineage. So there was one change recommend for the upcoming Southern Hemisphere season. Next slide. Okay. Again, this is an abbreviated presentation and discussion, but the Committee will discuss which influenza strain will be recommend for the antigenic composition of 2023 Southern Hemisphere formulation of influenza virus vaccines produced by licensed U.S. manufacturers.

Next slide. Okay. So, for the Southern Hemisphere strain selection, we do, as I said, an abbreviated version. We try to make it fairly simple, again, because there's only egg-based vaccines being produced by these two manufacturers.

We'll just take two votes; one, as shown on the top, will be for the composition of egg-based trivalent 2023 Southern Hemisphere formulations and will ask if the Committee recommends the same as what the WHO recommended, and that would be the inclusion of the A/Sydney/5/2021 H1N1-pandemic-like virus and, again, the same A/Darwin/9/2021 and B/Austria viruses

that have been recommended previously.

And then we'll take a second vote for the quadrivalent formulations, because manufacturers can make either a trivalent or a quadrivalent, and ask the Committee about including the B/Phuket/3073/2013-like virus for the B/Yamagata lineage as the second influenza B strain. And I think that's all. I can stop. If there's any questions, I'll be happy to answer them. Thank you.

Q&A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Weir. If you have any questions, there's a Raise Your Hand function in the Zoom with which I hope we're all familiar now. And I do not see any hands. Well, I do see a couple of hands. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you, Dr. Weir. I'm still a little bit puzzled about the need for the FDA to review vaccines that are going to be delivered in the Southern Hemisphere because the United States is

in the Northern Hemisphere. I know that these two companies ask for FDA approval, but don't the countries where the vaccine is going to be delivered have their own FDA, and are they using this FDA as a proxy for their FDA?

What's the reason for that? Why did they want the United States FDA to approve vaccines that will not be delivered in the United States?

DR. JERRY WEIR: Okay. So, yes, this comes up almost every year. It's sort of a two-part answer. I can't answer for every country. So some of them may want to do this. But you're right. A lot of them do have their own regulatory agencies. But the vaccine itself is licensed in the United States, produced by a U.S. manufacturer.

So that's why we go through the process, to make sure that, if they're producing this under their license, that they follow the procedure just like they do for anything else. But you're right; it probably does vary from country to country for how it is used and how that recommendation is used.

DR. JAY PORTNOY: But are they not allowed to produce the vaccines without FDA approval if it's not going to be given in the United States? Or do they have to have FDA approval just to manufacture it?

DR. JERRY WEIR: No. Okay. So, actually, I'm not sure I know the answer to that. I do think that these companies can make Southern Hemisphere vaccines without going through the FDA approval process. It's just, if they do it under their license, this is the process we have to follow.

DR. JAY PORTNOY: Okay. Thank you.

DR. HANA EL SAHLY: Dr. Bernstein.

DR. HENRY BERNSTEIN: Thank you for that overview, Dr. Weir. I just had one question, and that is what's the rationale for continuing to produce a trivalent influenza vaccine when it seems quadrivalent should be the direction around the world?

DR. JERRY WEIR: Well, you might get some pushback now whether quadrivalent is really that necessary, and I'm sure Dr. Wentworth will talk about that. Basically, that's a marketing decision.

Companies are licensed to produce trivalent or quadrivalent, and they can produce whatever they think that they can sell and they can market. In the United States, we don't force them to do one or the other.

But you're right; the trend has been toward quadrivalent vaccines for several years. And the amount of quadrivalent vaccines produced and utilized in the United States has, of course, gone up dramatically compared to trivalent. I think most public health officials would've said over the last few years that a quadrivalent vaccine is probably a better choice because the two lineages of influenza B have cocirculated for a long time.

But again, as you'll hear in a few minutes, that situation is somewhat changing. So we could be asking a different question before long about whether the quadrivalent really does have much of an advantage over the trivalent. Ever-evolving situation.

DR. HENRY BERNSTEIN: Thank you.

GLOBAL INFLUENZA VIRUS SURVEILLANCE AND CHARACTERIZATION

DR. HANA EL SAHLY: All right. With that sneak peek on the data, we now turn the meeting over to Dr. David Wentworth. Dr. David Wentworth is the Director of the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, and is the Chief of Virology Surveillance and Diagnosis Branch Influenza Division at the Centers for Disease Control and Prevention. Dr. Wentworth will go over the global influenza virus surveillance and characterization. Dr. Wentworth.

DR. DAVID WENTWORTH: Thanks, Dr. El Sahly. I'm going to walk you through kind of a brief version of what we discussed at the meeting. Actually, I kind of want to turn off my video before I start real quick here, sorry, just to make sure we have bandwidth. The one thing I wanted to mention is I've worked hard to make sure this is 508 compliant. If anyone that has vision impairments can't understand some of the slides,

please let FDA know, and we'll make sure we get that sorted out.

Okay. So the outline is to briefly describe the consultation meeting for the Southern Hemisphere 2023 recommendations and also a little bit about the influenza activity. I want to detail quite a bit about the H1N1 pdm09 viruses. That's the one that Dr. Weir mentioned has updated. We spent equal or more amounts of time on the H3N2 viruses and the B viruses, but we'll just cover those briefly because they remained unchanged. And I'll show you some data that relates to why they were unchanged.

So just a brief update of the meeting, it really benefits from continuous surveillance conducted by the Global Influenza Surveillance and Response System. This is a network of laboratories that I'll call GISRS all the time. Its birthday this year is a 70-year birthday, so it's been existing for a very long time, and it's played a huge role in our response to the SARS-CoV-2 Coronavirus 2 pandemic, or COVID-19 pandemic.

We have WHOCCs; which the CDC is one of them; and NICs, National Influenza Centers; WHO Essential Regulatory Laboratories, like the FDA; WHO H5 Reference Libraries all contribute. And we're supported by a number of countries and partners, over 150. The consultation was held from the 19th through the 22nd. It still remains a hybrid meeting. We had a couple of folks, Diana Wong, the CNIC director from China. And John McCauley, in the beginning of the meeting, he was also virtual, and he came towards the end.

It was chaired by Dr. Hideki Hasegawa, and I was the Co-chair. We have ten advisers, directors of WHOCCs and ERLs. Eight advise on seasonal influenza, and two focus on zoonotic viruses. I won't cover the zoonotic recommendations for pre-pandemic vaccines today. And then, you're used to all this. I see there are some new members, so I won't run too fast. There's 35 observers and experts from WHO regional offices and HQ. Dr. Weir just covered all this.

I won't belabor it. The big change was Sydney. We make recommendations for both egg-based

platforms and cell culture, or recombinant-based, platforms. And, even when viruses have the same name, like Sydney/5, there is a different protype often. There's a cell culture protype with a different accession number than the egg protype has. So there's sometimes isolate-specific differences.

And I wanted to point that out so that people can go to this technical report and go to the reagents part of the WHO recommendations and identify which may be the best for their cell culture or recombinant-based vaccines or if they're developing new vaccines. Now, we're going to stop and look at the number of influenza specimens that are positive. They have positive influenza specimens. And you can see we had this kind of flat period during the early stages of the COVID-19 pandemic.

And, as my English friends say, the last proper influenza season was January 2020. And you can actually see a rapid decline here as the COVID-19 pandemic came up. So there was definitely impacts by that. But now you can see that we're back and we had,

basically, two kinds of seasons, a smaller one in the Northern Hemisphere and then a little bit bigger one in the Southern Hemisphere. This is color coded, these bar charts. The light blue is H1N1 pdm09.

The kind of aqua color is H3. And the dark color is just not subtyped. B Vic lineage is the orange, and Yamagata, the light yellow. And B not determined is the darker burnt orange colors. That's just to give you a flavor. To get into the percentage of influenza A viruses by subtype and lineage, this pie chart illustrates it. And, over here, we've described it.

The specimens characterized between February and 30 August, 2022, 95 percent were type A, with 26, 27 percent of those being H3N2, and close to 2 percent, 1.7, being H1N1 pdm09, and 67 percent not-typed. For the B viruses, the 3.2 percent were type B. And all the samples that had lineage determined, which is 1.5 percent of the total samples, were B/Victoria lineage.

Now, this slide illustrates the global distribution of influenza viruses around the world

here, and it also has a key here where you can see the viruses by types, subtype in the various WHO transmission zones. And this is between February and August 2022. And you can see that, for the most part, there was a lot of type A and, often, it was H3 viruses. There were parts of Northern Africa where B dominated. And China had an interesting scenario where B initially dominated, and then H3 came in.

I'll move on. So I'm going to get into the H1N1 pdm09 viruses specifically. This slide shows the number of H1N1 pdm09 viruses detected by GISRS over the past four years. We have 2019 -- you can see it was a pretty normal-looking year -- 2020, 2021, and 2022. So you can see 2021, as we go through the year, and then we come into 2022 with the red line merging from yellow to red. We have basically very close to baseline.

This is a pretty big axis, 5,000 here, so you can see some blips. And it's actually moved up above the very flat line that it has. But H1N1 viruses has still been relatively rare compared to H3N2 amongst the influenza As, as I described on the earlier pie chart

slide.

Looking at where in the world H1N1 viruses circulated, this slide illustrates that. The percent positivity is color coded here on this key, with the light yellows being zero to five percent positive, a little bit darker, five to ten. And, as you get into the burnt oranges and the red, you're getting to 10, 20, and greater than 30 percent. So you can see, there was mild H1 activity in a number of countries around the world. And some countries, like South Africa, Kenya, France, had quite a bit of H1 activity.

Now, this is a high-level view of the phylogeography of the viruses. And this is provided by data, so all the CCs contribute along of genetic sequence data to GISAID and is pulled by our colleagues in Cambridge, Dr. Sarah James and Derek Smith. And we can do these very high-level trees, these mega trees. And, to the right of that, you can see a heat map illustrating which countries these viruses appeared in and in which months. And, at the top, I've labeled the year, so from 2019 through 2022.

So two major 6B.1.5a subclades emerged prior to the COVID pandemic, and its descendants continue to circulate. And two of these, 5a.1 and 5a.2, kind of made their way through the COVID bottleneck. So you can see that bottleneck here, just not very many tick marks in the 2020 era. Then, we saw emergence in Africa, for example, of 5a.1. So, over here on the far right, we have the key for the 5a.1, so they're this big branch of viruses, 5a.1s.

And, then, this big branch over here is 5a.2s. And you can see they were both cocirculating before the pandemic. The 5a.1s existed earlier, and the 5a.2s emerged later, and that lead to a strain change. So you can see that the 5a.2s have continued to diversify more where the tree if more flat in the 5a.1s. While they've continued to circulate, they haven't diversified as much genetically. I'll go into more detail in a closer-up tree next, but the 5a.2s circulated most recently in Oceania.

You can see this pink color. This is Australia. The green dashes are Europe. Orange is

Africa. And red is China and Asia in general. So you can see it circulating more globally. Whereas, the 5a.1s were primarily in Europe, a few detected in the U.S. or North America and, preceding that, quite a few in African countries.

Now, this is kind of important, so I'm going to spend a little bit of time on the H1 phylogeography of recent viruses and just walk you through this tree. So the previous tree was kind of driving down in evolution, where the two clades split. And this tree is now going up, really, from the older viruses being at the bottom. Idaho/7 was a previous vaccine virus, for example. It's way down here in the bottom.

So, in the bottom of this tree, we have the 6B1a.5a.1s, and I'll call them 5a.1s from now on. These often share this D187A and Q189E substitution. I've labeled here. You can see the small print. But this is where the branch point is for that D187A group. And all of these viruses are in that clade 5a.1. It's color coded by this pink bar here. We also to tick marks here. Now, this is just all 2022 from February

to August, so you can see which months these viruses circulated.

And you can see that a lot of these viruses circulated in Europe. But the tree is relatively flat, so they look very similar to viruses that circulated previously. We did have the emergence of these very unique groups that we pay a lot of attention to, this P137S and G155E, and that's like this North Carolina/02. And where we've labeled these viruses -- and sometimes I include them in the bullets here.

They're going to come up later on the human serology, and we always generally make ferret antisera and test a bunch of viruses against those as well. So this is a position of importance, 155 in particular. So we track those viruses very closely. Here, in 5a.2, represented by the A/Wisconsin/588 virus, that's the vaccine protype here in red, and the Victoria/2570. Wisconsin was the cell-based, and Victoria/2570, the egg-based.

These all share this group of substitutions here, labeled by the N156K, K130N, N156K, L161I, V250A,

and E506D, which is in the HA2 portion of the molecule. What you can appreciate -- this is a tree showing genetic distance -- is these guys have gone further genetic distance, as I've mentioned before. Now, nearly all the 5a.2 viruses circulated have at least these substitutions here characterized at this 186T mark, K154R, A186T, the Q189E, E224A, and then these other guys.

And they're really represented by this India/PUNE-NIV323546/2021, and so that's going to be one of the serology antigens I show you. They further diversified a very small subgroup identified in Africa, such as this A/Ghana/2871 has this additional changes at 137S and 142R, which actually preceded it in the evolution. Okay. So, recently, viruses primarily from Africa, Europe, and Oceania are seen there.

And you can see that again in the color coding here, whereas the color coding here is primarily Europe and Africa with a few in Oceania. I also wanted to point out the parallel evolution of 189E, and you'll see that better. But, basically, both of these

subgroups now, 5a.1s and 5a.2s, have acquired the 189E independently. Some people call that converge in evolution.

So this is one I rarely show. It's always one we look at. This is called a SeqLogo, so I'll walk you through this. I know some of you are probably familiar. We take all the samples collected from a certain timeframe in a window. Here's about 1,200 samples that we've sequenced since February. And it helps us start to identify positions under selection, so it doesn't really matter which clade they're in. We can see the position under section easier.

So the SeqLogo part of is the frequency of zero to one is shown here, and then the size of the letter for that particular amino acid at position -- 101 all the way through 250 is what I'm showing you here -- illustrates about what proportion in the virus population. It has that letter at that position. The other piece is underneath here. We're showing where the key antigenic epitopes are, antigenic sites on the HA molecules, so site Sa.

R stands for receptor-binding site. Ca is another epitope, Sa, Sb. Okay. So what I really wanted to point out is the defining mutations in the 5a.1 are position 156. And you can see an even split, really, here with the asparagine being the 5a.1 and the lysine being 5a.2. And they're smack in the middle of site Sa at 156. And then we see a little bit with 137S, but that's more contributed by the 5a.2. And 155E is probably very difficult to see here, but there's a tiny little E here.

So that's just telling you there's not much of that virus around. Now, with the 5a.2, the defining characteristics are that one 156K, as I already pointed out, 130N and 161I. So all of them will have that, but you'll also see the recent 5a.2 all have 186T, which you can see over here, and 189E. So this is what I meant about the convergent evolution. 5a.2s used to have the original amino acid there. But both the 5a.1s and 5a.2s now, in site Sb, have glutamic acid in that position.

Then we have the 224A, so you can see that

down here. That's in the receptor binding domain, and that can contribute to antigenic escape as well. So we pay attention to those. And, then, there's some parallel evolution, which I already mentioned.

So now, to help you identify where these are on the HA molecule, on the left-hand side, I'm showing you the India/Pune-NIV, which is one of our serology engines you'll see later and where the changes are relative to the Wisconsin/588 vaccine virus. You can kind of picture this. This bottom part here is where the virus would be. So the viral envelope is down here, and the HA goes up. And the HA1 top here, the head domain, which is the major antigenic site, is at the top of this molecule.

I'm only showing you a monomer for simplicity, but it's actually a trimer with all these changes in a trimeric feature. So what I wanted to point out was just some of these changes that we're seeing. The 224A, this is near the receptor binding site, so that's impacting that. The 186T and 189E are right up there in the head of the molecule in site Sb. And then

Ghana, which is that group I mentioned that had gone a little further evolutionarily, has all those changes and then has this 142R and 137S.

And they are in the site Ca, so I actually should've mentioned what these color codes are. This peach color here is site Sa. The blue color is site Sb. And the green is site Ca. And the yellow is site Cb. And these orange markings are glycosylation sites, and the red indicates amnio acid changes at those positions. So, really, all this is to give you a sense of there's important changes happening molecularly on the surface of the molecule in antigenic sites that we understand are important.

When we conduct antigenic analysis of the H1N1 pdm09 viruses across all the centers, which are listed here, we consider them either like or low to the vaccine. So two to four-fold reactivity patterns are considered like the vaccine or the serum from ferrets immunized with Wisconsin/588, for example, is neutralizing those virus as well. And, just when you get to the first deletion that would be some reductions

that you can really nail down as a eight-fold, that's where we start to wonder if the virus is escaping better.

So what you can see is, overall, nearly 80 percent of the viruses tested are reacting well to the Wisconsin/588-like virus. And the same is true for the egg-based Victoria antigen, and we're getting good reactivity there. One thing I would point out is the Francis Crick Institution; they're in London. They get a lot of viruses from Europe. And you can see it's a little bit different pattern there. Remember, they had a lot of 5a.1s in Europe, so this is a 5a.2 antigen. So, with ferrets, we would expect that to be a little bit lower.

Now, here, it goes deep into the data. I know no one likes to look at HI tables, but they're actually more informative than cartography. But it's easier to show cartography. I wanted to point out a couple of things on this panel. This is from our colleagues at VIDRL and the CC in Australia. Here, I'll just walk you through some of the sera and the reference

antigens. This is Guangdong-Maonan, so that's a 5a.1 virus. And the cell-based version of that is Vic2455.

In a Togo881, it's a little bit different flavor 5a.1 that was found in Africa in 2020. So we've got sera to each of those viruses. You can see their reactivity pattern highlighted in bold, so they have pretty good homologous titers. And then, when you test them against 5a.2, they're all below 80. So we get this very binary pattern.

In contrast, when we test Vic257 cell-based, which is basically the same as Wisconsin/588 -- that's their cultivar for the cell vaccine -- and then the egg-based Vic2570, see homologous titers here reacting very well with the 5a.2 viruses and not well with the 5a.1 viruses, and that's what I meant with the binary pattern. Here, we have Sydney5. This is the new recommended protype.

So you can see that that has a good titer and reacts very well with all the 5a.1 viruses and, again, poorly with the 5a.2. Now, while ferrets are a very good model for influenza viruses, we've known in most

recent years, particularly with the H1N1 pdm09 subtype of H1s, that they're immunodominant to site Sa, where the 156 changes, that the 5a.2 viruses have. And they don't react as much to site Sb.

So what you can see is, while the most recently circulating viruses from South Africa, for example, are reacting well here, when we look at the human sera pool from people vaccinated that included the Victoria/2570 vaccine -- this was an egg-based vaccine pool -- you can see some reductions in those most recent viruses. And we're going to get into more detail with that with the human serology studies, but I wanted to point it out here.

All right. So here's cartography. A lot of people like this because it's easy to differentiate what's going on. Hopefully you can see the light-grey squares within this box. They indicate two-fold reductions. So what we're doing here is comparing viruses to each other and to serum raised against different viruses. And this cluster's viruses is antigenically similar to each other or different from

each other.

Each light-grey square represents a two-fold, kind of, reduction or difference between the different viruses. Now, the color-coded viruses here, the red, is the 5a.2. They have the 156K. The green is 5a.1, which there's none on this map anymore. And the blue, for some reason the key doesn't show up right, but they're the 156N. They're shown here with the Guangdong-Maonan viruses. So clearly these are antigenically distinct groups of clusters of viruses.

And you can see this is all the viruses that were tested in the CC in Melbourne by hemagglutination inhibition since March 2022. And all the older viruses that had been tested previously are shown in grey, so you can kind of see where those two groups have been circulating for a while. So each virus clades clusters together. And, if you look at the Victoria egg, it's down here in the Sydney cell. The newly recommended vaccine is a little bit closer to the middle of the cluster, and here's the egg.

Now, here is adult human post-vaccination

sera, looking at the individual responses. So this is results from our Collaborating Center here. These are people that were immunized. These are a sera from Australia kindly provided by our colleagues in VIDRL. They were immunized with a cell-based vaccine or an egg-based inactivated vaccine, and then the elderly population had a adjuvanted egg-based vaccine. I'm just going to walk you through a few of these key features.

At the top, we're illustrating some of the key changes in the HA of the virus since the Wisconsin/588 cell-based vaccine, which everything will compared against here. So with the India/Pune, for example, here's the egg-based. It's Vic/2570. The next one over has the 186T, 189E, and 224A that I told you almost all the viruses share now. Then there's a Connecticut/01, which is just like that but has an additional change at 216, so one additional change.

And then there's the Ghana/2711 viruses, which have the 137S and 142 substitutions, so those site Ca substitutions. And then we also include 5a.1s. Those

are cocirculating. We saw a lot of those in Europe. These are kind of the older viruses. The previous vaccine for those was Hawaii/70, and so that's included as a serology antigen. And North Carolina/02 is one of the unusual virus with a 155E substitution. Note, that's just one amino acid away from 156, which we know is important as well.

So one of the things I want to point out with these individuals one -- and this is something that we're including in part because VRBPAC has asked us to show more on the human serology individual data; these are these bubble plots. The blue indicates pre-vaccination, what the individuals looked like. The size of the bubble indicates how many folks had that same, kind of, titer. And then the line with the number is the geometric mean titer. Okay?

So you can see the pre-vaccination, the geometric was, again, 588. The homologous antigen that they were being vaccinated with for Flucelvax, for example, was seven. And it jumped up to 188, so a pretty good response, with greater than 80 percent of

them having a four-fold conversions in titers greater than 40, which is a correlate of protection. I won't spend a lot of time on the Vic-egg virus, but basically similar results. And the other good news is the majority of viruses circulating look like this.

And we see a good response to those as well with the majority of people with a GMT of 153. And then the Connecticut, which has that additional change, a slightly lower GMT. And then we get into more reduction with the Ghana, and I'll show you this with some statistical power behind it. The other point I want to make is the back boost. So what you can see is these viruses, the 5a viruses before they diversified into the 5a.1s, circulated in our population in 2019, 2018, and 2020, in that period.

And they were in our vaccine. So, when we vaccinate with a 5a.2, we're actually seeing a pretty good boost against this unrelated clade that you would not see in a naive ferret, for example. So that's good news. And we actually see a pretty good boost of this new, very odd North Carolina/02 5a.1 virus. So that's

what I mean by the forward boost. So the forward boosting is these recent viruses.

We still get a boost. It's much better than not being vaccinated, where your GMTs are well below 40. And this is a basically similar pattern we see for IIV, not quite high as the GMT titers, and then the elderly population with the adjuvant. Sometimes, the elderly actually fare better with these back boost-type events. Okay. So the lowest GMTs were the Ghana/2711. I wanted to make that point, so I put it in the bullet.

Now, here we're looking at the results using a little bit more standard assay, and the statistical analysis of the GMT ratios are showing the inhibition by vaccine induced antibodies. And what you can see -- I'll just have you follow my pointer, which is an advantage with this particular presentation here -- these are GMT reductions versus the propagated cell Wisconsin, so we set that at 100, and all the responses.

What you can is, with the India/Pune, you get a little bit of a reduction in the 90 percent

(inaudible) interval shown on either side of that point estimate, in Connecticut, a slightly more reduction, and then, the Ghana, a more significant reduction, with this dash line being a 50 percent mark which we use to kind of really divide viruses from this noninferiority analysis. So all these viruses above the line would be considered noninferior, and this one below the line is potentially inferior.

So the vaccine would be potentially inferior for viruses like this. So the 5a.1, that's the similar phenomenon here. And then, again looking at the IIV4, we see the same pattern, different people, different vaccine, same pattern. The elderly, different people, different vaccine with different immune history, pretty much the same pattern. All right. So the India/Pune and Connecticut show modest reductions, and they have these changes.

And this is really what the majority of viruses have, these three that I've mentioned here, the 186, 189, 224. The additional changes kind of push it over the edge in the site Ca and drive that down. I

won't spend as much time on these. But the MHRA, which used to be the NIBSC, that are U.K. panels from the Northern Hemisphere and the same Southern Hemisphere serum provided by Australia, had a similar phenomenon with the Victoria/2570 egg being the one that they're testing against here.

Then, the Connecticut, which is the same virus we tested again, drops down. It's in this diamond. Okay. And then these in Trieste and Italy and Qatar also have a similar pattern; they have a similar look. And then the South Africa, which is like our Ghana strain, has this 137S and 142, you can see drops down quite a bit. So similar patterns across different centers with these different viruses. This is a compilation of all the data.

The blue means they're statistically noninferior, particularly if they have a checkmark in the box. As you get into the brighter orange, they get to be, basically, potentially inferior. Or the vaccine would be inferior for those antigens is a better way I should say that. So, in general, what you see is these

antigens that are the newer 5a.2 viruses are the ones where we're getting more of the orange across different centers, like the NIVSC or the CDC and other locations.

So to just summarize that clearly, it really shows that the 5a.2 genes have accumulated changes in epitopes, such as Sb, such that they better escape antibodies induced by the current vaccine antigens, and the additional changes at 137S and 142R in the site Ca further reduce the human antibody recognition. So to summary the H1s, globally, there were relatively few viruses with collection dates after January 2022 that have been detected.

But the great work of GISRS and all of our partners scour these viruses, send them to the WHOCCs, and we can do comprehensive analysis of what's circulating. The HA genes are all in clade 6B.1A.5a, which is the base clade of all of these viruses that I showed in my little tree over here. And they've split into the two subclades; 5a.1, which have that 187, 189 substitution, and they predominantly circulated in Europe; and the 5a.2, which circulated globally.

And we've gone over these amino acid changes, so I won't read them out, but that's the base. And, then, the majority of them now also have acquired an additional -- all have acquired these additional changes, the Q45, A186T, Q189E like the 5a.1, and the E224A, R259K, and K308R. A Sydney/5 is an example of a virus like that. It has a couple of addition mutations, such as the 216 substitution as well.

So, antigenically, this is the antigenic summary. Our analysis show that the 5a.1 and 5a.2 form two distinct groups. That's clear in the cartography. The ferret antisera to the Sydney/5 protype, both the cell and the egg, well recognized representative 5a.2 viruses, so contemporary 5a.2 viruses. And the analysis with the human post-vaccination sera showed that the 5a.2 HA genes have accumulated changes that facilitate escape from antibodies that are induced by current vaccine antigens.

And we saw that poorest inhibition with those that had the additional changes in that K142R and P137S. But they represent a very small proportion of

circulating viruses presently. So now onto the H3N2 viruses. This shows the number detected. It's the same kind of look we showed you for the H1N1, but you can see now these most recent periods. As we come out of 2021, we saw an increasing number. And, as you move into 2022, it started to fall.

And then, as the Southern Hemisphere picked up quite early and pretty much flatlined, this decline between weeks probably 31 and 36 is probably an artifact of reporting delays. So I wouldn't take that as a sharp decline being accurate. This slide, again, you've seen this before with the H1N1, shows the H3N2 activity. If you can remember back to that slide, that has a lot more light yellow in it. It's just illustrating how much more H3N2 influenza A viruses there were than H1N1 viruses.

You can see the countries and geographic regions in general where they circulated. In Northern Europe, we had quite a bit of virus around. I apologize. This download, there was a glitch in the WHO site. Australia should be almost red. It was

close to 30 percent positivity, if not more. So it's got a high amount of H3N2 activity, and they had a lot of viruses to analyze, our colleagues in VIDRL. So I apologize that's not indicated there.

You'll see that in some of the data with the phylogenies and the phylogeography that I'm going to show you here. So two major clades survived the bottleneck of COVID-19, the 2a1b.1s, which are the these red viruses, the small little group up here. And the reason these are all red dashes here are because they circulated in Asia and primarily in China. Then the 2a.2s really have a global distribution. I should've just kind of oriented you.

This 2a group is this whole bar here, the 2a1bs. 3C2a1b is the major clade. Then we're going to get into the 2a1b.2a.1, and I'll just call them 2a.1 and 2a.2. So you can see the 2a.2s just have this global distribution. Darwin/9 egg sits in the 2a.2 group, and Darwin/6 cell sit in the 2a.2 group. They were actually quite proximal on certain trees. This slide is a little bit easier to see. It's from our

colleagues at Nextflu, led by Trevor Bedford and Richard Neher and their colleagues I've listed here.

We work with them closely on fitness forecasting. Each of these Xs represents previous vaccine viruses, so it's a very simple tree to look at. It doesn't contain as much detail. But the 2a.2 viruses sit here in this kind of olive branch or brownish branch here. In the previous vaccine was the 2a.1 vaccine, the Cambodia/E08362. I've forgotten the last part of the number, but you remember the Cambodia vaccine.

And you can see that there's still some of these 2a.1 viruses circulating, and these were circulating as a time tree. These were circulating in China. But the vast majority of viruses circulating around the world are 2a.2s. And they've split into two kind of major subgroups; the D53G with the H156S subgroup, and that's this blue group here that Darwin/6 sits in, and Darwin/9 is right in there as well; and the D53N, H156S group, which is the green dots up towards the top.

Now, I'm not going to show you a really detailed tree with all the amino acid changes, but I will cover some of the important ones in the serology antigens. This shows you the clade turnover in the various countries which clades are circulating. Again, the pie chart's indicating 2a.2 being the dark green and the 2a.1 being the olive green. So you can just cast your eye across this entire map, and you really only see olive green in a few places. Timor Leste was one of them over here that has some of those viruses.

But they were primarily in China. The rest of the world saw 2a.2. This is analysis why ferret antisera to recommended vaccine antigens for the Southern Hemisphere 2022, which is the recommendation for 2023, Darwin/6, the cell-based, and Darwin/9, the egg-based. And what you can see is, across all the centers, we had really good data against this Darwin/6 antigen. So antisera to Darwin/6 neutralized the recent circulating viruses very well. Some centers had quite a few to test.

And this is just virus neutralization assay.

VIDRL tested many, many viruses as well by HI assay. I'm just not going to show you that data because it's very consistent with this. We do see a little bit of a decline in the egg-based antigen, and that's quite common in a H3 phenomenon. The egg-based vaccines have to acquire more amino acid substitutions to replicate the high titers in the eggs for the H3 viruses.

But it really shows there's not much antigenic drift going on. Even though we're seeing genetic changes, we're not seeing antigenic changes. And that's illustrated here in the cartography. So our colleague, Sarah James and Derek Smith at the University of Cambridge, take the HI and neutralization -- this is HI data from Melbourne -- that is produced and graph it for us so you can see this cartograph. And I'll spend more time on these 2a.2 viruses.

I can easily point out these are the 2a.1s down here where Cambodia/E0826360 -- that's the number I couldn't remember -- cell virus is sitting, right in the middle of a old 2a.1 virus, and just very few of those circulating. There was a 1a and a 1b still

circulating that our colleagues at VIDRL could test. But there's a lot of the 2a.2 viruses, and this is the position of the egg and the cell antigens in that cartograph. And then we have, broken out by color, whether they have the 156S, the 156S with 53N or 53G.

And what you can see is there's a relatively even mixture of those viruses in this antigenic space or this grouping. So there's not huge antigenic distinctions yet between those subgroups. That's what I make by this bullet point here. They're antigenically closely related. And really similar data was seen across the three centers here that I'm showing you, London again using HI. And then, CDC, we are using something called HINT, which is high contrast imaging neutralization tests.

So this is a virus neutralization test rather than a hemagglutination inhibition test. And it does provide a little bit more granular data, so you can see some separation of these groups that maybe are interspersed by HI. But they're still antigenically all closely related to each other. Now, human post-

vaccination sera. So the same sera that I described for the H1N1 viruses was used for the H3N2. And you remember the color coding we have here, blue being noninferior.

You're really looking at many flavors of 2a.2 viruses that were tested. The Darwin/6 is the homologous antigen that we're comparing to Flucelvax, for example, and we have Maryland/2 which has the 156S, 157L. These dominated the viruses in the United States last year. They were the predominant, kind of, subclade within 2a.2. We have Alaska/01, which has a carbohydrate change at the position 96, so that's sometimes a big deal, and the 192F. We see a minor reduction, but look at the GMT; it is still 113.

So that's not so bad. And then the Pennsylvania/01 is another subgroup. And the E50K, I should've pointed that out on the next strain view, but there was a small group of kind of purple viruses towards the bottom of that view, and that's what this one is. And there are not very many of these around, but we wanted to test them. And then we see, again,

good back boost against the 2a.1 Cambodia virus, so that's good.

So to summarize the H3N2, this predominated globally. Here's this little 50K virus group that I meant to point out before. The HA phylogenetics show that the HA of the majority of circulating H3N2 viruses are 2a.2. They continue to diversify. We've talked about these changes. Remember, the vaccine virus is in this group. So the HA subclade 2a.1 viruses really predominated in China, and that's the only place we saw them. They're clearly antigenically distinct, which I'm going to show you here.

Just to remind you what we cover, the ferret antisera against Darwin/6 and Darwin/9 really well recognized the majority of the viruses circulating in this period. And circulating 2a.2s are clearly distinct from 2a.1 viruses. The human serology studies show that the individuals vaccinated with the current vaccine viruses had good recognition and good neutralization of viruses with HAs from multiple 2a.2 subclades, for example D53N and D53G.

So now onto the influenza B viruses. Here, we're looking at the global circulation of the influenza B viruses from 2018 through 2022. Again, we have color coding with B/Victoria being green, so you can see the different epidemics when they're happening, B/Yamagata being flu, and a lineaging not determined being orange. And it typically corresponds proportionally if you were to do the lineage determination.

And, towards the discussion at the beginning of this meeting, we talked about Yamagata lineage. So the last, kind of, proper Yamagata epidemic was 2018. And the blue, you can't quite see it, but it's flatlined since then. What we've seen when we've seen influenza B, such as in 2020 and now in 2022, was B/Victoria viruses. So the focus will be on B/Victoria viruses. That's also illustrated here without the timing.

From February to August, all the viruses that had lineage determination, which was 79 percent of them, were B/Victoria viruses. There were zero

B/Yamagata viruses confirmed by a collaborating center. Sometimes there's some detections by PCR. But, when they're sent into collaborating centers, they can't be confirmed, either due to very high CTs or other issues. So here we're looking, again, at the activity around the globe, and we did see some good influenza activity for influenza B.

We have zero to five percent positive in a wide variety of countries across the globe. And then some countries, like in Africa, Egypt, for example, had a very high positivity rate. And I mentioned China in the beginning of the talk, where they had kind of an early season. There was a lot of Bs going around, and then it switched over to H3s. So China had a lot of B viruses, and they were all B/Vic. So we'll talk about the B/Victoria.

Again, it's quite a similar story across all the lineage I'm going to describe. We're kind of having two cocirculating primary clades that have kind of made their way through the COVID bottleneck. So, for the influenza Bs, the nomenclature is the main

clade, 1A, with a 3a subclade, and that was diversified into 3a.1 and 3a.2. And that's shown over here. So the 1A.3 emerged quite a while back. You can see them. They were a triple deletion variant, 162 to 164, which is an antigen loop in the hemagglutinin molecule.

And then there was some quiet time during COVID, and then it reemerged. In Asia, you can see quite a bit of these 1A.3 viruses with the 150K, 184E, 197D, and R279K. These then split into these two groups that it'll spend time talking about. The 3a.1s, which have the V220M and they primarily circulated in China, and the 3a.2, which really disseminated globally. It's kind of hard to see at this high-level tree. I'm going to dive you down into one of our trees that gets into some detail here.

We still have some older 1A.3 viruses, descendants of this 1A.3 group. So here's B/Iowa and B/Washington. B/Washington was the most recent vaccine in the 1A.3 group. We have some descendants related to that that were first identified in Kenya but then circulated more in the Netherlands recently. And you

can see those, in April, May, and June, they were detected. And they've acquired a couple of additional changes.

So I'm pointing those out because they kind of still are hanging around, and they've acquired additional changes. So we're going to include this B/Kenya in the serology data I'll show you. The 3a.1, as I've already mentioned -- you can see all this red here -- they primarily circulated in China. They have this V220M that I boxed in red and P241R. And it's represented by the Sichuan-Jing yang/12048/2019 virus, and you can see they've continued to circulate a bit.

And then they've also got in China, now, a turnover. So they've really replaced the 3a.1 viruses with 3a.2s, which are categorized primarily by these first branch of the tree at the A127T, P144L, K203R. So they're listed here. The B/Austria is kind of near the base of that group. Okay. That's the current vaccine recommendation and the vaccine recommendation for 2013 for the Southern Hemisphere.

In China, they've acquired primarily -- we see

them there -- these H122Q, so that's included as a serology antigen, the B/Henan-Xigong -- pardon my pronunciation -- will be there. And then we've seen further evolution post the 182, 197E, 221 grouping here, represented by B/Maryland for example. And then a lot of them had this D197E, so parallel evolution at that site. Very small change, aspartic acid to glutamic acid, with the Massachusetts/1.

So I think I've covered all the things in these bullets here, which are to help people that have visual impairments as well. Okay. So the global B/Victoria HA clade diversity here. What I'm illustrating or what we are trying to illustrate, I should say, is the period from September 1st to January 1st and then the more recent period, and just trying to illustrate how the clades have changed in various countries. The main one to focus at is kind of the decrease in this 3a.1, the dark blue viruses in China.

They represent about a quarter of the pie in this period. And, also, some continuing lingering of the V1A.3 base clade viruses, but really a more swing

over to more 3a.2, which are the aqua colored viruses. And you can see that in the same country. It's always nice when you're looking at viral fitness to have viruses that are cocirculating in the same counties even and the same countries.

And this is an easier way to see that clade turnover, but it doesn't show you the geography of the clade turnover. So you can see early, February 1, at this time last year, this period last year for 2021, there was a lot more 3a.1 viruses around, and they just continued to decrease to about five percent now. And the 3a.2 viruses have continued to increase. And there's just a few of these base viruses hanging around.

Antigenic analysis, again using the vaccine antigen sera as a summary for the cell and the egg, again good matching here between the cell and the egg across most of the centers, even CNIC now. Previously, they had a lot more of those, the 3a.1 viruses, but now they have more of the same types of viruses we're seeing globally. And you can see 92 percent of the

viruses are well recognized by sera against the B/Austria. And that same is true for the B/Austria egg component.

Here is some nice cartography illustrating this group here, the V1A.3. Here it's 3a.2 in that, kind of, green color. And then some of the breakdown of the 3a.2 with 122Q, which you can see a lot of in the Beijing data and not very much to that in the data from the Atlanta CC, so our data. Then, we also have the 3a.2 with the 197E. We had more of that to test. So you can see good clustering against this B/Austria egg isolate with quite good antigenic recognition.

Clear antigenic distinction from the previous group of virus, the 3a viruses, the Washington/2-like viruses. And the other thing I wanted to point out, we don't have any of these 3a.1 viruses for us to test at the CDC, but they're here. So you can see a clear antigenic distinction between the 3a.2 and the 3a.1 as well as the base 3A. So you can see that antigenic split in the two different groups.

The CDC, we don't have those 3a.1 viruses, but

we did have some of this unique groups with the 155A that I pointed out, like the Kenya virus or in the Netherlands. So you can see that's pushing down a little bit away from this cluster but not hugely different. So to dive into really a big overall summary from multi-centers for the human post-vaccination serologic analysis, again using sera from the most recent vaccine panel provided by Australia. Volunteers, adults for Flucelvax and IIV4 in elderly.

And, really, what you can see is there's a lot blue in this whole 3a.2 region, even those that have additional substitutions that we selected. And where you start to see some of the orange, so potential inferiority against those antigens, you can see that they're the rare antigens, like the Kenya virus that I pointed out and in some of the 3as, 3a.1s.

So what this shows is that the current vaccine antigens elicit antibodies that well inhibit the majority of recent representative B/Victoria lineage viruses from the 3a.2 subclade. So B/Yamagata, there have been no confirmed detections of circulating

Yamagata since March 2020, therefore, there is no B/Yamagata/16/88 lineage viruses that have been available for analysis by any of the collaborating centers during this period. To summarize the Bs, only Vics have been circulating as I just said.

Parts of Asia and a few countries in Africa had a higher percent positivity. The HA phylogenetics really illustrates that all of them belong to 1A.3, which has this major deletion at 162 to 164 and the K136E substitution. A small number of those continued to circulate and have diversified a little bit further, and they were identified in Kenya and the Netherlands.

A subclade the 1A.3a viruses that encode the 150K and G184E and N197D substitutions along with the R279K have predominated and split into two subclades, with the 3a.1 subclade seen exclusively in China and diminishing or decreasing in number, and 3a.2 seen globally really -- I've just listed every place there -- with the majority of them now having D197E either alone or in combination with other changes. Antigenically, the subgroup 3a.1 and 3a.2 are clearly

distinct.

You can remember that from the cartography. What illustrates that is really the post-infection ferret antisera, and it really shows that the vast majority of recently circulating viruses are well inhibited by that antisera but that antisera poorly inhibits the 3a.1 viruses. In a small number of the 1A.3 that were detected in Kenya, Netherlands are still circulating, and they were not well recognized by sera against the B/Washington-2, the older vaccine virus.

And they're even recognized more poorly with antisera against the B/Austria 3a.2-like viruses. So they are quite distinct. To summarize the human serology, the post-vaccination sera, this is again using the Southern Hemisphere panel, which included B/Austria-like viruses, it really well inhibited the majority of recent representative B/Victoria viruses from the 3a.2 subgroup.

Yet, there was some significant GMT reductions detected in serum panels from the small group of viruses from the 1A.3 that had those additional

changes, characterized by the 155A that I highlighted. That concludes my presentation, and I'm happy to take questions.

Q&A SESSION

DR. HANA EL SAHLY: Thank you, Dr. Wentworth. I invite my colleagues to start using the Raise Your Hand function to ask questions to Dr. Wentworth, and I'll kick us off with a few I had. The first one is the cartography charts prepared by the Cambridge lab, are they based on ferret sera or human sera?

DR. DAVID WENTWORTH: They're based on ferret sera.

DR. HANA EL SAHLY: Okay.

DR. DAVID WENTWORTH: And that's because we can get that -- now I can talk and use my hands.

DR. HANA EL SAHLY: Yes.

DR. DAVID WENTWORTH: I'm a hands person. You can get that separation. With human sera, if you remember, I showed you those. We use a 50-percent

mark, which is a really, really high bar, so that's really only two-folds reduction. With ferret antisera, you can get these 8, 16, 32-fold reductions because they're naive ferrets. They also are kind of interesting animals in that they really kind of hyper focus antibodies on parts of the HA. Basically, they can see changes that humans don't see.

They can see single amino acid changes. So it provides very granular data. You get these very pretty cartography graphs. If we do that with a human sera, everything is just fuzzy and merged together because they're only about two to four-fold apart, unless it's an unusual situation. And then, the other thing that I should mention, with very young pediatric sera, that does look a little more like ferret sera.

We didn't have that from the Southern Hemisphere, but we have that from when we do the Northern Hemisphere recommendation. The CDC acquires a sera from the pediatric sera, basically, 6 to 36-month-old individuals.

DR. HANA EL SAHLY: Actually, that gets to the

other question I had, which is the H1N1. There was the cocirculation of the a.1 and a.2. Using ferret sera, there was a significant difference in the responses between these two. But, on the last hand panel of your chart, the differences were minor with human sera. So I just wonder if there are any data on, for example, pediatric mortality and hospitalization, sort of like a (inaudible) for the clinical meaningfulness of these differences.

DR. DAVID WENTWORTH: Yeah. There is data. We publish on the FluView the pediatric deaths that are reportable when they're coded as influenza. Unfortunately, the H1N1 tends to have more fatalities in the pediatric population that the H3N2. So we always are quite cognizant of that with the vaccine viruses selected. To answer your question "why was it fuzzy in the human sera," it's really because the 5A viruses, which preceded the 5a.1s, and 5a.1s have a little bit more minor changes comparatively to the 5a.2 viruses.

So, previously, in our population here and in

the population in Australia, these 5A viruses circulated. And the vaccine was a 5A or a 5 virus, so I'm just going backwards in time. Then, they also had a 5a.1 vaccine. If individuals have either seen the virus, been infected by the virus, or had the vaccine, when we vaccinate with the 5a.2, there's so many shared epitopes. You saw there's only like five red dots on that molecule, so that's 500 amino acids on that molecule.

So there's so many shared regions. Sometimes people say back boost, but your B-cell memory sees those and responds. And that's what I was showing where you see those GMT titers pretty high to an out-of-clade group. If we were take a group that never circulated, that's when you start to see taht reduction, even in humans. You kind of saw that, for example, with the Ghana virus. That really hasn't circulated.

There's very few of those around now. Neither group of people that would have high titers to the 5a.1s or the 5a.2s reacted that well to that Ghana

group for example.

DR. HANA EL SAHLY: And did I read your slides correctly in that there was back boost with the H1N1, but not with the B/Victoria?

DR. DAVID WENTWORTH: The B/Victoria, yeah, that's true. So the B/Victorias, because those were all -- if we had included Washington in there, you would've seen it. But because the 3a.1s, the China viruses, those -- I probably shouldn't have said it that way. But the virus that circulated predominantly in China, those are really antigenically distinct from the progenitor and so are the 3a.2s. They both split and went different directions.

So we include those because they're contemporary and it doesn't boost against those. Actually, you nailed it. That's a perfect example of it's not a back boost because both of those are antigenically distinct and they're antigenically distinct in different ways. Whereas, in the other example, with the H1s, a lot of viruses like those viruses have circulated previously.

That's partly what drove the selection of the 5a.2s in the first place as a vaccine, because we have that anticipation that there's going to be a lot of back boost, and we had some data from human serology that illustrate that. When you have two groups that are cocirculating, which one am I going to lean towards? The fact that there's not a huge risk in the human population of the 5a.1s because a lot of people still have preceding memory against it. Whereas, the 5a.2s are newer to our immune system.

DR. HANA EL SAHLY: Okay. We have questions from our colleagues, beginning with Dr. Offit.

DR. PAUL OFFIT: Thank you, David for that very clear presentation on a very difficult subject. I have two questions, if that's okay. The first is it seems that we've largely eliminated or dramatically reduced B/Yamagata, presumably because that strain is less capable of drifting than, say, the other three H3N2, H1N1, and B/Victoria. If it came to be that we just only had a trivalent vaccine, that we eliminated B/Yamagata, would that virus eventually reemerge?

DR. DAVID WENTWORTH: I can't answer that question, Paul. It's a great question. B/Yamagata can evade immunity pretty well. So I have a whole theory on why B/Yamagata disappeared. One of the issues that we've have, that we've discussed quite a bit once we get out decisions made is about B/Yamagata. We had discussions within the WHO. One of the issues we've had is very low-level circulation of all influenza since COVID-19 pandemic.

As everyone is quite aware -- I'll use the analogy of iceberg -- there's a very big iceberg of flu out there, and we only see the top part of that iceberg. To declare Yamagata dead, I would like to have more of a B season. I'd like to understand we have a huge denominator. One of the things we're doing in the U.S. with our state public health lab partners is strongly encouraging lineage testing. It's an extra test. They don't really have to do it.

You can prescribe antivirals just knowing it's influenza A or B. You don't know have to know it's Victoria or Yamagata. Through the International

Reagent Resource funded by the CDC, we're pushing out lineage tests to all 50 state public health labs, or 64 actually. We're going to try to do as much lineage testing as we can. So we have a big denominator where we've tested a lot of viruses, and they were all B/Victoria and none were Yamagata.

DR. PAUL OFFIT: One last question, if that's okay, Hana.

DR. HANA EL SAHLY: Of course.

DR. PAUL OFFIT: It looks like, with Flucelvax as compared to the egg-based vaccine, as you said, when you grow these viruses with mammalian cells, there's less of a difference between the virus that you started with, the vaccine virus, and the vaccine virus that you end with. Associated with that, it does look like there's a better match in terms of hemagglutination and inhibition titers. Would we ever get to a point where Flucelvax would be a preferred vaccine?

DR. DAVID WENTWORTH: You're asking me the hard questions that I can't answer. I don't know about that either. That becomes a regulatory question, I

think. I have groups of 20 individuals here in each of the age groups, or maybe 40, depending on which serum panels we're looking at. So it's not the kinds of numbers and it's not the number of seasons. So I'll kind of give you that answer. I think it's possible.

If you really look at it, it should work better. I just should, but we haven't really seen VE (phonetic) be hugely different, and there hasn't been a lot to studies in the real world that go to that. I think I'll probably just stop there. But I think the disappearance of B/Yamagata holds hope that, if we have a great vaccine and we had a worldwide vaccine distribution, we could actually impact flu virus, stop it.

DR. PAUL OFFIT: Thank you.

DR. HANA EL SAHLY: I would qualify that by saying there was a pandemic in the middle. So that could be a huge confounder.

DR. DAVID WENTWORTH: Part of the B/Yamagata disappearance was B/Victoria. So it almost acted like a vaccine. B/Victoria had two huge waves because of

huge antigenic drifts. There was a double-deletion mutant that preceded the triple-deletion mutant which preceded the COVID pandemic. So, if you'll remember those peaks, you didn't see any B/Yamagata, even before COVID.

So, probably, the combination of a natural wave of -- and influenza A does this too. H2N2 wipes out H1N1, and then when we have a new pandemic. So it may have been something like that.

DR. HANA EL SAHLY: Okay. Dr. Berger.

DR. ADAM BERGER: Thanks so much. David, great presentation, really clear here. I think you've already addressed, partly, the question I wanted to ask, so I'm going to put a little bit more specificity on it then. It's the Yamagata strain, and it's mostly just because of the fact that you're not detecting or you're not identifying any samples.

I do note that the February 2022 WHO report does note that there were reports of Yamagata, but they were unconfirmed. I think we had this same exact scenario come up in the March meeting when we set the

vaccine for this fall. I guess the question I have is why can't we get access to those samples where they're claiming that it's Yamagata, or they're identifying that it's Yamagata, but it's untested and unconfirmed?

DR. DAVID WENTWORTH: Yeah. I think that is a language issue. So the majority of them have been sent to collaborating centers, either the National Influenza Center or the state public health laboratory where they were initially detected. When they can't be confirmed, that is either when the collaborating center does the diagnostic, real-time PCR, it doesn't come up as Yamagata, or all of them have been not able to be propagated.

So they've been such high CTs that they're barely at the limit of detection, and they haven't been able to be propagated. Those that have been, there's been a few that are likely from kids that were vaccinated in the days preceding swabbing with live attenuated vaccine. So that will also pick up the Yamagata.

DR. ADAM BERGER: Thanks. That's actually --

DR. DAVID WENTWORTH: Sometimes it's confirmed as live attenuated. And often we can't confirm it by real-time PCR or sequencing.

DR. ADAM BERGER: Appreciate it. And I think this goes back to the original question around the quadrivalent, which is, I think, on all of our minds. Do we continue to include Yamagata? Or do we, for instance, move to including a 5a.1 variant that would be much more potentially helpful and protective since the cross reactivity with the Sydney (inaudible) and the 5a.2 and the 5a.1 would be very limited? I think that's the question we're all trying to get at at the end of the day. Thank you so much.

DR. DAVID WENTWORTH: I appreciate it.

DR. HANA EL SAHLY: Dr. Perlman.

DR. STANLEY PERLMAN: Nice talk, Dave. So I actually was going to ask the same question that Adam asked at the end. I have a corollary of that question. So when you think about these vaccine formulations, is there a way to do any calculation of the probability of being right or being wrong? So for the 5a.1, 5a.2,

both circulating, 5a.2 is more dominate. Does the CDC ever do a kind of calculation to say that this has a 93 percent chance of being right or 50 percent because that would help inform this question of --

DR. DAVID WENTWORTH: Right.

DR. STANLEY PERLMAN: -- what do put in a quadrivalent.

DR. DAVID WENTWORTH: Yeah. Well, historically, I think the team -- it preceded my time, so maybe I can say this. Historically, when we used to only have a trivalent, sometimes it would seem like B/Victoria should be in the vaccine, but it would be a B/Yamagata year. Historically, it hadn't been great. We do do a lot more now with fitness forecasting.

We work very closely with Trevor Bedford and Richard Neher, and we also work with Marta Luksza and Michael Lassig, who both have different types of fitness forecasting systems. They are part of the meetings, so we do do that. It's not quite the statistical probability that you're talking about because it's quite a challenge. So how that fitness

forecasting is working is taking into account genetics.

It's taking into account something called local branching index, which is how many viruses are changing within that particular subclade. And it takes into account hemagglutination inhibition and neutralization tests as well as positional changes within the HA. The issue with flu, it's quite different from SARS where you don't get a complete sweep.

SARS may actually end up going more like flu where we always seem to have many cocirculating subclades, and it becomes quite a challenge, unless you have a trajectory that's very obvious. Typically, the forecasts indicate both will continue to circulate. They're confident of that. Then, one may be higher than the other, so that's the kind of data that we're generating there.

DR. STANLEY PERLMAN: Okay. Thank you.

DR. HANA EL SAHLY: Dr. Monto.

DR. ARNOLD MONTO: Hi, Dave, great presentation. I'm not going to be asking about the Bs,

which really are unanswerable. Although, I think it's going to be necessary to bite the bullet fairly soon, especially given the fact that, when we did the vaccine effectiveness studies, there seemed to be reasonable cross protection, even though there shouldn't have been. But we rarely couldn't distinguish, even in children, that giving the wrong trivalent selected vaccine made a whole lot of difference.

I'm uncomfortable when there isn't diversity in the A H3N2s. My question is we had early seasons in the Southern Hemisphere. And you came up with the iceberg analogy in terms of getting a number of strains in. Did we have and have (inaudible) isolates from the Southern Hemisphere been processed yet? How comfortable are you with not changing the H3N2, which is almost unprecedent?

DR. DAVID WENTWORTH: Yeah. I think that the comfort level with not changing the H3N2 is pretty good. I agree with you. This is the virus that is the most challenging, and to get to Dr. Perlman's question earlier, it's the most unpredictable, even when you

think you know what's going. Fortunately, there was a lot of data from the Southern Hemisphere. The Australia had an early season. South Africa had an early season. Actually, South America had a really atypical season the year before.

So the 3a.2s, the good news is there is some genetic diversity there. And you can see some of those amino acids are probably having an impact, but it's really minor, both in the ferret antisera and in the post-vaccination human sera. So one of the things that we're seeing with this particular antigen is really quite good geometric mean titers, so it's a pretty good antigen too. So that also helps, that you can kind of cover drift better if you have a higher titer. It's kind of the idea of boosting.

DR. ARNOLD MONTO: I'm glad you mentioned the antigenicity because that's often something we ignore when we look at the (inaudible).

DR. DAVID WENTWORTH: To dive into this, in particular for you and some of the other afficionados on the call, the 2a.1s and the 2a.2s -- I'm just

dropping the front part of that name, the 2A1b part. But the 2a.1s maintain a glycosylation site at 158. And that glycosylation site has been critical in antigenic escape from the human immune system, and that's why it evolved in 2014. So it's been there since 2014. The 2a.2s lost that site. But, underneath it, they had changed a lot of amino acids.

That site, basically almost -- I don't know how to say it really, but you can imagine. And it has asparagine-linked glycan at the top of the molecule. It really shields the molecule from antibodies for the most part. So it made those vaccine antigens just harder to be good antigens. This is getting a little hand-wavy, but basically that's true. We see higher titers, even in the ferrets, with the 2a.2 viruses because they're now more naked at the top of the head of the molecule.

So there's quite a bit of those circulating. And, as you saw in the high-level trees, they are diversifying. But the data we have says that the ferret antisera covers that diversity pretty well. And

then, the human serology data, remember all the blue in that statistical analysis -- and I didn't go into as much detail on the H3s as I usually do in the human serology. But it's pretty good reactivity there. We haven't seen really what those changes are.

You could also do it geographically. Each of those groups, because we've had, I think, limited travel, they're really very geographically oriented. They're like little islands, like founder effect-type things, where you can see these are South American viruses. These are European. These are North American. So we had to scrounge around in the U.S. to find some of the examples that would be in the other parts of the world.

DR. HANA EL SAHLY: All right. Thank you, Dr. Bernstein.

DR. HENRY BERNSTEIN: Thank you, Dr. Wentworth. I'm not an aficionado, or I don't consider myself. So I always learn a lot in listening to your presentation. I had a couple what are probably basic questions for the aficionados. You mentioned way back

at the beginning when there were 95 percent As and 3.7 percent Bs. With the type As, you mentioned only one-third of them are typed.

Is there a minimum percentage that need to be typed in order to interpret all the results that you've given? Or would it have changed if two-thirds have been subtyped?

DR. DAVID WENTWORTH: Yeah. It's a interesting question. I understand where you're coming from. It's quite a few viruses, even though it's a small percentage or whatever that are typed. So generally, if you take a certain region and try to use that as a microcosm, you see a very similar ratio. Because we didn't do it, I really can't say for sure that it wouldn't be that different.

But I think, in general, we have -- how it works is determining whether it's influenza A or B is two PCR tests, generally, for most these labs that are participatory. And then, in order to do the subtyping for A, they have to do another set of PCRs. Or, for lineage testing, they have to do another set of PCRs.

So it creates additional work. So, typically, what they do is just a subset of the viruses that they're analyzing on a regular basis are subtyped or lineage determined.

And that's why you get this falloff where a bunch of them aren't.

DR. HENRY BERNSTEIN: Okay. And then I had a second question, and that is can you comment a little more on neuraminidase inhibitors susceptibility of these different subclades and all that you've presented to us?

DR. DAVID WENTWORTH: Yeah. So did you notice I left that out of this presentation?

DR. HENRY BERNSTEIN: I certainly did.

DR. DAVID WENTWORTH: I usually include it.

DR. HENRY BERNSTEIN: It was in the pre-read, but I didn't hear you comment about it.

DR. DAVID WENTWORTH: Yeah. I'm sorry. Because this was a vaccine strain selection, I decided, well, it's vaccines. It's not really therapeutics. But we didn't see -- there were five that were

resistance to neuraminidase inhibitor. And, oh, my goodness, I'm going to have to remember which subtype it was. It was H1N1, but out of close to 900. So it's quite rare. I remember 0.6 percent.

And then we didn't see others in the other viruses of note that were tested. So we're in pretty good shape on the medical counter-measure part with both baloxavir, which is a PA inhibitor, and with the neuraminidase inhibitor, such as oseltamivir.

DR. HENRY BERNSTEIN: That's helpful to us clinicians.

DR. DAVID WENTWORTH: Yeah. I could include it. Just, for time's sake, I dropped it out of all sections.

DR. HENRY BERNSTEIN: No, I appreciate that. It was in the pre-read. I thank you.

DR. HANA EL SAHLY: any additional questions from the Committee members for Dr. Wentworth. I do not see anymore raised hands. Thank you, Dr. Wentworth, for this presentation and for the members for the engaging discussion. Next on the agenda, we have a

ten-minute break. It is 9:15 Central time. Let's reconvene at 9:25 Central time. Thank you, all.

[BREAK]

OPEN PUBLIC HEARING

DR. HANA EL SAHLY: All right. So, welcome back to the members, the audience, and the participants on this 177th meeting of VRBPAC. Currently, we have on the agenda the Open Public Hearing session. There were no individuals who signed up for the OPH session. Hence, we will not have any items to go over in this session.

That takes us to the Committee Discussion, Recommendations, and Voting.

COMMITTEE DISCUSSION, RECOMMENDATIONS, AND VOTING

DR. HANA EL SAHLY: So we will be discussing first what we heard and then voting on the questions, and each one of us will briefly explain why they voted.

I will start off the discussion by indicating that Dr. Wentworth's presentation was very clear and informative as usual. The Yamagata situation is very intriguing. It began before the pandemic, and then we

had three years of unusual lack of circulation of influenza, lack of human travel, and closing of schools, all sorts of incubators that allow the flu epidemiology to be what it is usually.

So, it'd be interesting to follow that story going forward now that a lot of the non-pharmacologic methods of controlling the COVID pandemics are going away. The H1N1 -- the diversification, certainly, by ferret antisera is concerning and would potentially justify the change in the strain proposed.

Of course, as more data are emerging from Southern and Northern Hemisphere, it'd be important to see how this translates clinically, in terms of VE and severe disease outcomes. Dr. Portnoy.

DR. JAY PORTNOY: Okay. Great. Thank you. Yeah, I guess my only comment is that I'm not really sure how effective these vaccines have been at preventing disease. So, I would like to see, in the future, information that describes the epidemic of the vaccine with the influenza of patients who received the vaccine versus those who did not.

Did the people who were vaccinated -- did they get different strains, or were they more or less likely to have infection? We've never really seen a comparison between those who were vaccinated and those who were not. And if we don't have individual patient information, at least information about vaccine prevalence in different countries, how many people were vaccinated, and what effect that had on the influenza epidemic that occurred that year -- I just haven't seen that information.

And I guess I would love to see that in the future because it would help to determine how effective our selection of these strains actually has been on modifying influenza disease.

DR. HANA EL SAHLY: So, Dr. Portnoy, during our spring meetings, we do hear those data pertaining to vaccine effectiveness using a test-negative design. Well, most of the presentations are from the CDC, and some are from the Department of Defense, who has a bigger global footprint in that domain.

So, in essence, this is a shortened meeting.

But those data, we heard them this past spring, and we will hear them in the coming spring meeting.

DR. JAY PORTNOY: Okay. Yeah, I don't remember the details, but I look forward to that. Thank you.

DR. HANA EL SAHLY: You're welcome. Any other comments before we proceed to the voting? Please use the "Raise your Hand" function. I'm going to try and see. Okay, Sussan, I don't see any raised hands from my colleagues, so if you don't mind putting up the questions on the screen so we proceed with voting.

I will read the voting questions. We will begin with Question 1. Sussan, we're going to vote 1, then I read 2, we vote 3? Or do you want me to read both? Which is more streamlined?

DR. SUSSAN PAYDAR: Actually, Hana, if you don't mind, I'll read the instructions first before we move on to the voting. These were the voting questions for the discussion. So, for now, I'll just read the instructions, and then we will move on.

"Only our 14 regular members will be voting in

today's meeting with regards to the voting process. Dr. El Sahly will read the final voting question for the record, and afterwards, I'll ask all regular voting members to cast their votes by selecting one of the three voting options, which include "yes," "no," or "abstain."

"You will have one minute to cast your vote after the question is read. Please note that once you've cast your vote, you may change your vote within the one-minute timeframe. I'll announce when the voting poll has closed. At that point, all votes will be considered final. Once all the votes have been tallied, we'll broadcast the results and read the individual votes aloud. This is for the public record."

Does anyone have any questions regarding the voting process before we begin? And just so everybody knows, the non-voting attendees will be moving to a separate waiting room for a minute or two while we are holding the voting session. So, please be patient. Do not log off. We will be back once the voting is done

and everything is final, so hold on.

DR. HANA EL SAHLY: Sussan, if I may, we have two of our Committee members having questions, beginning with Dr. Berger.

DR. SUSSAN PAYDAR: Yes.

DR. ADAM BERGER: Hi. I just had a question about Question 2 because it only has the option for the inclusion of the Yamagata strain. And I'm just curious, if the Committee were to vote no, would we be, then, having another question as to what we would be recommending for inclusion?

DR. SUSSAN PAYDAR: That is a question Dr. Weir might want to address.

DR. JERRY WEIR: Yeah. Typically, what we do is that we give the Committee the option if, for example, you do not agree with the question that is posed, the Committee members can propose something different, and then we would formulate a question. Yes. That would be the way it would work.

DR. ADAM BERGER: Thanks.

DR. HANA EL SAHLY: Dr. Portnoy.

DR. JAY PORTNOY: Yeah, just a brief question about procedure. In order to vote, this is a different system. Do I understand that we use the reactions and either click on the green arrow or the X arrow? Or how will the voting actually take place?

DR. SUSSAN PAYDAR: I'll defer this question to Derek. Derek, you want to walk us through it a little bit?

MR. DEREK BONNER: Absolutely. So we will be using the polling system that's completely built inside of our Zoom platform. Whenever we do launch the voting question, a poll will pop up on your screen where you will have the option to choose "yes," "no," or "abstain." Once you submit your vote, that's all you have to do. The rest of us will take it from here for displaying results. Thank you.

DR. SUSSAN PAYDAR: Great. So, now, if, Derek, you could put the Voting Question Number 1 so Dr. El Sahly could read Voting Question Number 1 for the record.

DR. EL SAHLY: Voting Question 1, "For the

composition of egg-based trivalent Southern Hemisphere 2023 formulations of influenza vaccine, does the committee recommend: inclusion of an A/Sydney/5/2021 (H1N1) pdm09-like; inclusion of an A/Darwin/9/2021 (H3N2)-like virus; and C, inclusion of a B/Austria/1359417/2021-like virus of the Victoria lineage?"

MR. DEREK BONNER: We are ready to display.

DR. SUSSAN PAYDAR: Great. Thank you so much, Derek, for this smooth transition. So there are 14 total voting members for today's meeting. We have a unanimous vote for yes. Here are the voting responses of each of the voting member. I'll read them aloud for the public record. If you could display the Excel for everyone to see, Derek, that would be fantastic. Okay. Let's see if I can close this one. Great.

All right. Here are the voting responses, as you all can see. I will read them aloud for the public record. So, one by one. Dr. Andi Shane, yes; Dr. Eric Rubin, yes; Dr. Hayley Gans, yes; Dr. Holly Janes, yes; Dr. Arnold Monto, yes; Dr. Hana El Sahly, yes; Dr. Paul

Offit, yes; Dr. Hank Bernstein, yes; Dr. Jay Portnoy, yes; Dr. Archana Chatterjee, yes; Dr. Amanda Cohn, yes; Dr. Steve Pergam, yes; Dr. Stanley Perlman, yes; Dr. Adam Berger, yes.

Thank you so much. At this time, I will hand over the meeting to Hana again. If you could, please go ahead and read the second voting question. And, Derek, if you could, please display the second voting question for everyone to see.

DR. HANA EL SAHLY: Voting Question 2, "For the quadrivalent 2023 Southern Hemisphere formulations of influenza vaccine, does the Committee recommend the inclusion of a B/Phuket/3073/2013-like virus (B/Yamagata lineage) as the second influenza B strain in the vaccine?

DR. SUSSAN PAYDAR: Great. Thank you, Hana. I'll wait for Derek to give us the signal when all the voting members are (audio skip).

MR. DEREK BONNER: We are ready to display.

DR. SUSSAN PAYDAR: Great. Thank you, Derek. There are a total of 14 voting members for today's

meeting, voting second question. I'm going to be reading the votes. We have a total of ten who voted yes, two members who voted no, and two who have abstained. If you could display the total results, that would be fantastic. Great. Thank you so much.

Here are the voting responses. I'm going to read them aloud for the public record. Steven Pergam, yes; Stanley Perlman, abstain; Dr. Jay Portnoy, yes; Dr. Hank Bernstein, yes; Dr. Hayley Gans, yes; Dr. Archana Chatterjee, yes; Dr. Arnold Monto, abstain; Dr. Amanda Cohn, yes; Dr. Holly Janes, yes; Dr. Eric Rubin, yes; Dr. Hana El Sahly, yes; Dr. Paul Offit, no; Dr. Adam Berger, no; Dr. Andi Shane, yes.

Okay. That concludes the voting portion for today's meeting. I'll now hand over back the meeting to Dr. El Sahly for asking the Committee for their vote explanation. Thank you so much.

DR. HANA EL SAHLY: Sure. Thank you all. So I'm going to try and display the screen in a way that allows me to see the members. Okay. So we'll go over the room to explain the vote. I will begin with my

vote.

As I indicated, the epidemiology of Yamagata is intriguing. I hesitated between yes and no on that one, but I finally decided on a yes because the last three years were unusual, in terms of human behavior, travel, schools, social mingling, et cetera. The disappearance of Yamagata occurred in this setting, or at least this particular setting confounded what we are observing quite a bit.

The next year would be critical to determine whether the Yamagata is of any usefulness as the fourth strain. We debate every year the H3N2 situation, and next year may be a critical one in determining what we do with the B and potentially preparing for another fourth strain that is of more clinical value. Dr. Bernstein.

DR. HENRY BERNSTEIN: Thank you. As far as the B, I voted yes because I agree that the pandemic has been a significant confounder, and I don't think that it would make sense necessarily to shift course given the pandemic. I do think that we should change

the H1N1, the first question, because I felt that the ferret antisera and the human serology studies suggested the need to change the H1N1 component, which is why I voted yes there.

DR. HANA EL SAHLY: Thank you. Dr. Monto. You're still on mute.

DR. ARNOLD MONTO: Okay. It worked finally. I am cognizant of the Hollywood quote from the 1940s, "If you want to send a message, call Western Union." But I think we need to begin to think about what will happen if we want to go to remove the B/Yamagata. We've had this discussion now for a year or so. We've had some reasonably large B outbreaks from certain countries -- from China, I believe also from France, some other countries -- where B has really transmitted.

Also, the B strain we're being asked to put in the vaccine, the B/Yamagata, is a 2013 virus. If the virus is out there lurking somewhere, I'm not sure it's going to resemble a 2013 virus at this point given the kind of evolution we've seen.

I think we really need to start including

regulatory thinking about what will happen, what is necessary, to include, for example, two H3N2 strains, the ones that worry us most and the ones which we have the lowest vaccine effectiveness.

So, that explains my abstention. I think we really have to put this on the front burner. And it is going to take a while, so we need to start thinking about it now. Thank you.

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

DR. STANLEY PERLMAN: Yes. I agree with most of what's been said. I abstained on the second vote for the same reasons that others have talked about, whether the Yamagata strain should be included and whether we should, if we could do a quadrivalent, have it be an H3N2 or an H1N1 quadrivalent.

So, I would just like to continue probing with this. But I didn't say firmly no because of all this uncertainty about the Yamagata strain.

DR. HANA EL SAHLY: Dr. Berger.

DR. ADAM BERGER: Sorry. I was trying to get off mute and get my video working. So I definitely

agree that the COVID pandemic has been a confounder here for us. However, in my view, the vaccine's really going to only be as good as we can adduce immunity to the circulating strains. I really would've preferred to see a 5A1 in addition to the 5A2 that we approved in the first question to try and offer the best protection we can to individuals this year.

Now, I think it is a question we need to make sure that we address in the future. It's going to come at some point, I think, giving us the opportunity to address more strains that are circulating or that present greater issues, as Dr. Monto just noted with the H3N2. I think that really frees us up to be able to try and get a much more effective vaccine going.

So, that's why I voted no for this round -- was, if we have no detected Yamagata strain going around, we've not been able to have a confirmation for two and a half years at this point, the protection that that offers is going to be minimal in my opinion. So, that's the reason why I voted no. Thanks.

DR. HANA EL SAHLY: Dr. Cohn.

CAPT. AMANDA COHN: Thanks. I also agree with everyone else's comments. I voted yes. Frankly, could have abstained, could have voted no for all the reasons that have been said, but I do feel like this was a decision that has been made by WHO and that this is for the Southern Hemisphere.

I think it would be challenging at this time to differentiate from those recommendations that were made by WHO, and I feel like we need to push for a better understanding and sort of determine what would replace -- if we decided to replace -- Yamagata in the spring for next fall.

DR. HANA EL SAHLY: Dr. Offit.

DR. PAUL OFFIT: Yeah. Thanks, Hana. I agree with everything that's been said. I think we're not going to get much bang for our buck by including the Yamagata in the quadrivalents vaccine, and I do think we would get larger bang for our buck if we sort of covered our bets on H3N2. But, that said, I think that is a separate discussion.

I think we need to have a much longer

discussion about what that means for the companies, what that means in terms of the way that these vaccines are licensed because it's really a dramatic change. And I do think we would be better off with that than we are with this.

So, I think we should, in the future, really create some time for us to have that kind of serious discussion about moving to this different strategy. Thank you.

DR. HANA EL SAHLY: Dr. Weir. Well, let's save -- Dr. Weir, (inaudible).

DR. JERRY WEIR: Yes. I would rather go at the end, Hana. Thank you.

DR. HANA EL SAHLY: Okay. Good. I was just going in order here. Dr. Rubin.

DR. ERIC RUBIN: Paul just said everything that I would say. I think this vote is -- everyone agrees, and they voted yes, abstain, or no with the same feeling. I think we really do have to think about what a vaccine with two H3N2s would look like, but now is probably not the right time for it. But very soon,

we should be having that discussion.

DR. HANA EL SAHLY: Let's see, the members -- Dr. Pergam.

DR. STEVEN PERGAM: Yeah. I don't really have any additional comments other than what has been said. It is interesting that we'll be talking about the North American strain soon, so I think having these discussions about what's going to be in the vaccine will be important as we begin to talk about this in -- I guess it would be later in the spring. I think this will become maybe more relevant at that time once we see what happens with this year.

I voted yes because -- it's more to what Amanda said -- it feels strange just sort of voting against it at the moment. But I think part of the voting from others seems to be more of just a comment to say we need to be discussing this. So, I think we all agree on that point.

DR. HANA EL SAHLY: Okay. Dr. Shane.

DR. ANDREA SHANE: Yes. Thank you very much. First of all, I just also wanted to thank Dr. Wentworth

for the fabulous presentation. I always learn so much, and it's really greatly appreciated.

I voted yes to both. I agree also with everything that has been said. I am a little bit concerned that we may see more Yamagata, and I was also a little bit concerned that there was a large proportion of Bs that were not actually strain-specified. So, that was my other reason for voting yes, but obviously, I agree that we need to have some further discussions about composition in the future. Thank you very much.

DR. HANA EL SAHLY: Thanks. Dr. Janes.

DR. HOLLY JANES: Thank you. Generally agree with what has been said, I think. I voted yes given the data that are available and the uncertainties that remain in the context of the pandemic, and fully agree with all the comments about the need for additional time for deliberation, perhaps separate deliberation, around mixing up the composition of flu vaccine strains and how we should view that as a new framework. Thank you.

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

DR. ARCHANA CHATTERJEE: Yes. My reasoning for voting yes was very similarly based on the data that were presented and the same concerns that have been raised by a number of the members already. The one additional thing I will say is that -- I think Steve Pergam referred to the meeting we will have in the late winter or early springtime to decide on the Northern Hemisphere strains to be included -- I'm not sure that we will have a great deal more data to make those decisions on.

And, so, I think this discussion that Dr. Offit and several other people have referred to about including another H3N2 strain probably does need to be had sooner rather than later if we are in need to change the composition in this major way. This hasn't been changed for many years now, and it's time to have that conversation sooner rather than later, I would say.

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

Portnoy.

DR. JAY PORTNOY: Great. Thank you. I agree with what everyone else has said. The trivalent vaccines seem to be pretty clear and uncontested. I think the data was very strong. As everyone else mentioned, the Yamagata strain, it's unclear. But, as Paul Offit mentioned, we don't know what the risk is of it reemerging if we stop giving the vaccine. At least, that was in response to this question.

And I would really hate to vote no and then see it reemerge as a result, especially since we just don't have that much information about how it has behaved during the pandemic. I'd like to see a regular year. The fact that Yamagata is in this year's vaccine means that we're not going to really know what happens if it's not included in the vaccine in February when we have our discussion about it, so we're really not going to have that information.

The only way we're going to find out if we really need to kick Yamagata is to take it out of the vaccine and see what happens. I'd hate to do that, but

that probably is the only thing that the Committee's going to be able to do.

I think the fact that there have been a couple of no votes this year, when there have never been any before, sends a strong message -- or at least it should send a strong message -- to the CDC and to the companies that they need to look into the option of including something other than the Yamagata strain for the quadrivalent for next time and at least have that option available as something to consider and to discuss.

I guess one question I do have that I'm not sure what the answer is: does the fourth strain have to be a B vaccine, or can it be an A strain? Is it possible to have three A strains and one B, or does that fourth one have to be a B for regulatory purposes? I don't know the answer to that. But thank you.

DR. HANA EL SAHLY: Dr. Gans.

DR. HAYLEY ALTMAN-GANS: Thank you. I really do agree with my colleagues, and I think that my vote was yes because I think that really, for reemergence,

we've seen different patterns than we've seen previously. Therefore, there's plenty of naive people who are coming into this.

Only one comment that hasn't been brought up, obviously, is the pediatric population, which I think we have to continue to consider, just because they are obviously, as Dr. Wentworth had pointed out, more like the ferret and naive to this, so they would follow more of that. And when some of those levels dropped, it was a concern. So, I do think that those conversations do have to appear in how we can protect these vulnerable populations.

I do think that making predictions and -- I mean, I'm hoping that everyone's vote is as loud as everyone else's and that we're all sort of in agreement that the composition needs to be carefully considered every time we do this. And we have had the fortune of not having circulating strains in the last two years. That doesn't mean we can, with that amount of accuracy, really tell us what strains.

And I would agree with Andi that -- I also

noted that there were some -- at least in the Bs, it was a very small portion of those that were serotyped. And Dr. Wentworth responded that that is true, however, these have largely been predictive in the past. We just don't know. So, that was where my votes were yes for those.

DR. HANA EL SAHLY: Okay. I think all the Committee members had the opportunity to weigh in. So, to sum it up, the Yamagata strain inclusion is more questionable. Some of us hedged on the yes just because we had two to three years of unusual epidemiology that confounded the findings and the small proportion of B that has been circulating. But this year, maybe, will be more of a regular flu season.

If anything, it's also in the Northern Hemisphere early and strong. Texas is up and running already; I can tell you that. So, hopefully, when we meet in the spring, we can have better data and larger sample sizes that will allow a better determination in terms of inclusion of H3N2.

Dr. Weir/Dr. Wentworth will weigh in. But, to

my knowledge, there are no human data on the quadrivalent with the fourth being an H3 or an H1, but every year after this meeting, I try to probe and I get nowhere. So, maybe this year is the year. Dr. Wentworth.

DR. DAVID WENTWORTH: Thanks very much. I think you kind of caught on what I was going to comment on. Number one, I want to thank everyone on this Committee. I really appreciate your questions and probing questions with regard to the presentations and always want to do our best to give you the data there. And I think having Dr. Weir after me is very good because he can tell you some of the regulatory perspectives.

I wanted to bring in some of the discussions we had in the WHO meeting as well regarding this. So, just from my perspective, in the killed vaccines, there's almost zero downside in including a Yamagata lineage. I understand the reasons for a vote or an abstain or a no to kind of get people thinking, we could do something else. But I agree with Dr. El

Sahly.

We don't have preclinical data in animals with two H3s that I've seen, and you don't know if your immunodominance is going to be messed up. So, you don't know that, by including two different clades of H3, which I think would be the most likely scenario, that you would actually end up with better broadly cross-reactive antibodies. You might end up with antibodies that are more to the conserved portions that are the same in both molecules and actually reduce stimulating antibodies to the new epitope.

I think that's one of the problems with flu vaccine. We give the vaccine and people have seen the virus before, and we get a very small prime to that new epitope. We get a very big memory response to epitopes we've seen before. And that prime is very difficult to cause protection from infection. It helps protect from disease. So, I really think that needs to be thoroughly investigated.

And people come and say, the CDC should do this. It really -- this becomes an academic question,

and it's also a company question. They need to have a license for a product like that, and Dr. Weir will cover that. When we talked to the WHO, there's two currently licensed thing -- well, multiple currently licensed things, but they are trivalent or quadrivalent. So, for a quadrivalent vaccine, the license thing right now is a B/Yam and a B/Vic. And so, really, to me, I think the question is which B/Yam to put in there.

And apparently, B/Phuket's a fantastic antigen because it's wiped out the Yamagata, right? So, I mean, I'm being facetious there. But there really isn't much of a choice regarding that to me. You have a quadrivalent vaccine. We don't have data on another Yamagata to substitute for the 2013. There's been a couple in 2020, but there wasn't really great data that they would be better than Phuket.

So, I'll just put those two things in perspective for you from our perspective. And I do think we really need a bigger denominator of the number of viruses that have been lineage-tested. We're really

trying to get that.

DR. HANA EL SAHLY: Thank you, Dr. Wentworth. Dr. Weir.

DR. JERRY WEIR: Well, first of all, thanks to everyone. This has probably been the most interesting Southern Hemisphere discussion we've ever had. Usually, our discussion of the Southern Hemisphere is fairly straightforward, and it serves mostly -- or for at least some of us -- as a preview of what will be discussed a few months later for the Northern Hemisphere. I think, this time, the Committee has really done a great job of honing in on some of the bigger questions that we are going to have to wrestle with.

So, just to clarify a few things -- and David did this already, but I'll restate it -- yes, companies are licensed to produce trivalents and quadrivalents, but only in the formulations that we already know -- one H1, one H3, for a trivalent 1B, or for a quadrivalent for 2Bs. So, any changes to that general composition would require a change to each

manufacturer's license. And changes to manufacturer's license require data.

So, I couldn't agree more with -- I think it was -- Dr. Portnoy that said something about he hoped companies were listening. I do, too. Those companies could be thinking now about what sort of trials they would need to do to show, as David Wentworth pointed out, that there's no interference, that the inclusion of two H1s or two H3s doesn't adversely affect the other one. Those are the type of data that probably will be needed before we can make a general composition change of the type of strains that are included.

So, yes, this is going to be interesting going forward. We don't know what's going to happen to B/Yamagata; only time will tell. And maybe in the next six months, we'll know more. But these are big important questions of how one improves the influenza vaccine, and I think it's great that the Committee has pointed this out.

I think these are important questions, and we are going to need some more data to make these sort of

fundamental questions. And it could be that this is the sort of thing that, in next March, we end up discussing, on top of our usual, which strains should be included. So I'll pause there. If anybody has any last-minute questions for me, I'll try to answer or clarify my comments. Over.

DR. HANA EL SAHLY: Thank you, Dr. Weir. I guess one important consideration now is it seems that the season is going to be more active this year. And more complete typing or representative typing would be quite helpful in that domain, in addition to companies and research institutions beginning to probe the preclinical and clinical values of including a fourth strain that is either an H3N2 or a divergent H1N1. Dr. Monto.

DR. ARNOLD MONTO: I just want to reiterate the fact that we all agree. Even though we have voted differently, I voted abstain because of all the issues that Dr. Wentworth and Dr. Weir brought out. But we need to address them. We really haven't addressed them as yet, and a lot of it, I think, is due to our

concentration on the COVID pandemic so that the march to a better influenza vaccine really has been forgotten for a little while.

We need to get back to that, and we need to begin to look at the immunodominance issues that Dr. Wentworth raised. As we talk about this, we have to consider also that we have a variation in the kinds of flu vaccine we have. If we go to a two H3N2 component in our regular vaccines, what happens to the high-dose vaccine? So, it's a complicated issue and will require a lot of study and discussion, and we need to start it now. Thank you.

DR. HANA EL SAHLY: Dr. Portnoy.

DR. JAY PORTNOY: All right. Yeah, thank you. I just had one final comment. I just got my flu vaccine two weeks ago, and my understanding is that vaccine hesitancy for influenza vaccine has increased along with COVID vaccine hesitancy. Partly because of that, I'm hoping that the American public seeing how carefully this Committee reviews the strains and the data regarding the vaccine will encourage people to get

their flu shots because it really is important.

If people don't get the flu vaccine, all the work of this Committee is for naught. It's a safe vaccine. It can be highly effective, and it's very carefully decided. So, I'm hoping that vaccine hesitancy doesn't prevent people from getting their flu shot. Thank you.

DR. HANA EL SAHLY: Thank you. Okay. So I'll turn the meeting over to Dr. Paydar.

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DR. SUSSAN PAYDAR: Thank you, Hana. I would like to ask Dr. Marks for his closing remarks. Dr. Marks.

DR. PETER MARKS: Thanks very much. Just want to say thank you to everyone for the conversation and the dialogue this morning. I do think it was probably the most exciting Southern Hemisphere meeting that we have had. So, thank you for that. I think it does actually show that we are paying attention here, and I

think we'll look forward to our Northern Hemisphere discussion in a few months.

But I just want to thank everyone for their thoughtful comments and really appreciate everyone's participation today. And thanks to members of the public who tuned in. Also, very importantly, thank you to Sussan and others from the Advisory Committee group who helped put this together. I really appreciate that. Thanks very much.

DR. SUSSAN PAYDAR: Thank you, Dr. Marks. Thank you all for closing comments. I wanted to thank the Committee and the CBER staff for working so hard to make this meeting a successful meeting. I now call this meeting officially adjourned at 11:12 a.m. Eastern Time. Have a nice day, everybody.

[MEETING ADJOURNED FOR THE DAY]