Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

184th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

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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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Chair

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Temporary Voting and Non-Voting Member		
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Consumer Representative		
Jay M. Portnoy, M.D.	Professor of Pediatrics University of Missouri – Kansas City School of Medicine, Director Division of Allergy, Asthma, and Immunology, Children's Mercy Hospital and Clinics	Kansas City, MO
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David Greenberg, M.D.	Interim Vaccines Medical Head North America, Sanofi	Swiftwater, PA
Anthony Fries, Ph.D.	Public Health and Preventative Medicine Department, DoD Global Respiratory Pathogen Surveillance Program Lead U.S. Air Force School of Aerospace Medicine Wright-Patterson	Air Force Base, OH
Lisa Grohskopf, M.D., M.P.H.	Medical Officer, Epidemiology & Prevention Branch Program Lead Influenza Division, Centers for Disease Control and Prevention	Atlanta, GA
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David C. Kaslow, M.D.	Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD
Jerry Weir, Ph.D. (Speaker)	Director, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD
Sudhakar Agnihothram, B.Pharm., Ph.D.	Associate Director of Office Regulatory Initiatives, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD

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Call to Order

Dr. El Sahly: I would like to welcome the members, the participants, and the public to the 184th meeting of the Vaccine and Related Biological Products Advisory Committee. During this meeting, we will be discussing an open session and making recommendations on the selection of the strains to be included in the influenza virus vaccines for the 2024/2025 Northern Hemisphere Influenza season. I would like to remind the committee members and the participants to use the raise your hand feature and turn their camera on if they have a question or comment to make, and then I can call upon them to speak. I would like to introduce now Dr. Sussan Paydar as the designated federal officer for today's meeting, Dr. Paydar.

Administrative Announcements

Dr. Paydar: Great. Thank you, Dr. El Sahly. Good morning, everyone. This is Sussan Paydar, and it is my great honor to serve as the designated federal officer for today's 184th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA, the Center of 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 and make recommendations on the selection of strains to be included in the Influenza Virus Vaccines for the 2024/2025 influenza season. Today's meeting and the topic were announced in the Federal Register Notice that was published on February 9th, 2024. At this time, I would like to acknowledge outstanding leadership of Dr. Peter Marks, Director of Center for Biologics Evaluation and Research. Dr. David Kaslow, Director of Office of Vaccines Research and Review. Dr. Weir, Director of Division of Viral Products, OVRR. and Dr. Sudhakar Agnihothram, Associate Director of Office Regulatory Initiatives, Office of Vaccines Research and Review.

I also would like to thank my Division Director, Dr. Prabhakara Atreya, for her excellent leadership, and my team whose contributions have been critical for preparing today's meeting: Ms. Valerie Vashio, Ms. Joanne Lipkind, Ms. Kathleen Hayes, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to AB team, Mr. Joseph Ely, Mr. Derek Bonner, and Mr. Gideon McMillan 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 FDAomaa@fda.hhs. gov. The transcriptionist for today's meeting are Catherine Diaz and Deborah de la Crocce from Translation Excellence.

Roll Call

We'll begin today's meeting by taking a formal roll call for the committee members and temporary voting and non-voting members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, institution, and areas of expertise. 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. Hanna El Sahly.

Dr. El Sahly: Good morning, Hanna El Sahly, Baylor College of Medicine. I'm an adult infectious diseases physician and my areas of research are clinical vaccine development.

Dr. Paydar: Great. Thank you, Dr. El Sahly. Dr. Adam Berger.

Dr. Berger: Hi, I'm Adam Berger. I'm the director of the Division of Clinical and Healthcare Research Policy at the National Institutes of Health. I'm a geneticist by training with additional training in immunology. Thanks.

Dr. Paydar: Thank you. Dr. Henry Bernstein.

Dr. Bernstein: Good morning. I'm Hank Bernstein. I'm from a professor of pediatrics at the Zucker School of Medicine at Hofstra North Shore. And I am a general pediatrician with expertise in vaccines.

Dr. Paydar: Thank you so much. Dr. Archana Chatterjee.

Dr. Chatterjee: Good morning, everyone. My name is Archana Chatterjee. I have the honor and privilege of serving as the Dean of Chicago Medical School and Senior Vice President for Medical Affairs at Rosalind Franklin University of Medicine and Science in North Chicago.

I am a pediatric infectious diseases specialist by background and training with expertise in vaccinology. Thank you.

Dr. Paydar: Thank you, Dr. Chatterjee. Next is Dr. Haley Gans.

Dr. Gans: Good morning, everybody this is Dr. Haley Gans pediatric infectious disease professor of pediatrics at Stanford University. I'm also the director of our pediatric infectious disease program for immunocompromised hosts and my area of research is in immune response to vaccines and special populations. Thank you.

Dr. Paydar: Thank you. Dr Holly Janes.

Dr. Janes: Good morning. I'm Holly Janes. I'm a professor of biostatistics at the Fred Hutch Cancer Center in Seattle with particular expertise in vaccine evaluation.

Dr. Paydar: Thank you. Next is Dr. Louis Jodar, our industry representative.

Dr. Jodar: Good morning everybody. I'm Luis Jodar. I'm the Senior Vice President and Chief Medical Affairs Officer for Pfizer Vaccines and Antivirals, and my expertise is in vaccinology and infectious diseases. Thank you very much.

Dr. Paydar: Thank you. Next is Captain Sarah Meyer.

Capt. Meyer: Hi everyone. My name is Sarah Meyer. I'm the Chief Medical Officer in the Immunization Services Division at CDC. I'm a pediatrician and I have expertise in vaccines.

Dr. Paydar: Thank you. Next is Dr Arnold Monto.

Dr. Monto: I'm Arnold Monto at the University of Michigan School of Public Health in Ann Arbor, and my interests are in epidemiology of respiratory infections and in vaccine evaluation. Thank you.

Dr. Paydar: Thank you so much Dr. Monto. Dr. Paul Offit.

Dr. Offit: Good morning. I'm Paul Offit. I'm an attending physician in the Division of Infectious Diseases at Children's Hospital of Philadelphia, and a professor of pediatrics at Penn's Medical School. My area of interests are mucosal vaccines and vaccine safety. Thank you.

Dr. Paydar: Thank you, Dr. Offit. Next is Dr. Steven Pergam.

Dr. Pergam: Hey, Dr. Paydar. It's Steve Pergam from the Cancer Center in Seattle, Washington. I'm a professor and I'm interested and focus my research on immunocompromises.

Dr. Paydar: Great. Thank you so much. Next is Dr Stanley Perlman.

Dr. Perlman: Good morning. I'm Dr Stanley Perlman. I'm in the Department of microbiology and immunology at the University of Iowa. I'm a long-term corona virologist and I'm a pediatric infectious diseases specialist.

Dr. Paydar: Thank you so much, Dr. Perlman. Next is Dr. Jay Portnoy, our consumer representative.

Dr. Portnoy: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics and I specialize in allergy immunology at Children's Mercy Hospital in Kansas City, Missouri.

Dr. Paydar: Great. Thank you so much. Next we'll do a roll call of our temporary voting member and temporary non-voting member. Colonel Douglas Badzik, our temporary voting member.

Colonel Badzik: Good morning, everyone. Doug Badzik. I am a preventive medicine physician. I'm also the director of a health readiness policy and oversight for the Department of defense. Thank you.

Dr. Paydar: Thank you so much. Dr. Rebecca Kondor, our temporary non-voting member.

Dr. Kondor: Good morning, everybody. My name is Rebecca Kondor. I am currently leading as the interim director of the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at the Centers for Disease Control within the National Center for Immunization and Respiratory Diseases and Influenza Division.

In the Influenza Division, I lead the Genomic Analysis Team within the Virology, Surveillance, and Diagnosis Branch. Studying the genetic and antigenic evolution of influenza viruses.

Dr. Paydar: Thank you so much, Dr. Kondor. Thanks everyone. We have a total of 15 participants, 13 voting and 2 non-voting members now proceed with reading the FDA conflict of interest disclosure statement for the public record.

Conflict of Interest Statement

The Food and Drug Administration, FDA, is convening virtually today, March 5th, 2024. The 184th meeting of the Vaccines Unrelated Biological Products Advisory Committee (VRBPAC) under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Hana El Sahly is serving as the voting chair for today's meeting today on March 5th, 2024, the committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2024/2025 influenza season. This topic is determined to be a particular matter involving specific parties, PMISP. With the exception of industry representative member, all standing and temporary 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 laws, including but not limited to 18 USC 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 US Code 208, their employers. These interests may include investments, consulting,

expert witness testimony, contracts and grants, cooperative agreements, 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 members are in compliance with federal ethics and conflict of interest laws under 18 USC 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 services outweighs the potential for a conflict of interest created by the financial interest involved. Or when the interest of a 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 on all financial interests reported by committee members and consultants, no conflict-of-interest waivers have been issued under 18 US Code 208 in connection with this meeting. We have the following serving as a temporary voting member: Colonel Douglas Badzik, the OD representative. We also have Dr. Rebecca Kondor from CDC serving as a temporary non-voting member and speaker for this meeting. As a temporary non-voting member, Dr. Kondor is not only allowed to respond to the clarifying questions from the committee members, but also authorized to participate in committee discussions in general. However, she's not authorized to participate in the committee voting process.

Dr. Louis Jodar will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee.

Dr. Jay Portnoy is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their

participation in the meeting. They are voting members of the committee. Disclosure of conflicts of interest for speakers and guest speakers follows applicable federal laws, regulations, and FDA guidance.

The guests and industry speakers for today's meeting are as follows: Dr. Lisa Grohskopf, medical officer in the epidemiology and prevention branch influenza division at the Centers for Disease Control and Prevention, Atlanta, Georgia. Dr. Anthony Fries, DoD Global Respiratory Pathogen Surveillance Program Lead, United States Air Force School of Aerospace Medicine, Wright Patterson Air Force Base, Ohio. Dr. David Greenberg, Interim Vaccines Medical Head, North America, Sanofi. The speakers have been screened for conflicts of interest and cleared to participate as a speaker for today's meeting. As guest speakers, Drs. Grohskopf and Anthony Fries are allowed to respond to the clarifying questions from the committee members following their presentations; however, they're not authorized to participate in committee discussions or to participate in the committee voting process. Dr. David Greenberg is serving as a guest speaker from industry to provide flu vaccine manufacturers perspective to the committee. Dr. Greenberg is allowed to respond to the clarifying questions from the committee members following his presentation; however, he's not authorized to participate in committee discussions.

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 standing and temporary members 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 the discussion, 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 our chair, Dr. Hana El Sahly. Thank you.

Dr. El Sahly: Thank you, Sussan. The introduction of the meeting will be given by Dr. Jerry Weir. Dr. Jerry Weir is the director of the viral products at the Vaccines Research and Review Office at CBER FDA. Dr. Jerry Weir.

Introduction: Jerry Weir, PH.D.

Dr. Weir: Thank you and good morning and welcome to our annual influenza vaccine strain selection meeting for the Northern Hemisphere.

As we do this every year, the purpose of these meetings are to review the influenza surveillance and epidemiology data, genetic and antigenic characteristics of recent virus isolates, serological responses to current vaccines, and the availability of candidate vaccine strains and reagents. And after that review, the committee is asked to make recommendations for the strains of Influenza A H1N1 and H3N2, and Influenza B viruses to be included for this year for the 2024/25 Northern Hemisphere formulation of influenza vaccines licensed for use in the United States.

The next slide shows the agenda, which you're already familiar with, but just briefly following this introduction, you will hear about the US influenza virus surveillance data and global. Influence of our surveillance and characterization. These will be given by our colleagues at CDC, and you'll get a report from the Department of Defense influence of our surveillance, as well as some of their mid season vaccine effectiveness data. And then finally, you'll get a brief update about candidate vaccine strains and potency reagents that are available and comments from manufacturers representative, then the committee will discuss what they've heard and go through the voting, which I will get to at the end of this introduction.

Okay, so as I said, we do this every year about a year ago and March 7th, in fact, we met following the WHO recommendations for their Northern Hemisphere influenza vaccine composition for the current season, 2023/24 season. I'm not going to read all of these voting questions about the composition because we'll get to the more recent ones in a minute. But the most interesting aspect of the

meeting a year ago was the voting. And when we did the voting the votes for the H1N1 component, the H3N2 component, and the Influenza B Victoria lineage were all unanimous. But the committee voted for the inclusion of a B Phuket virus, but the vote was, I think it was seven yes. And then there were six either abstains or no votes. And at that meeting a year ago, the committee expressed some level of discomfort with the inclusion of a fourth strain, a second B strain. At that time, they had been presented with data that indicated there had been no B Yamagata viruses for nearly three years. And they expected us to discuss this in future meetings, which we have.

So if you go to the next slide, fast forward to October of this past year when we met for the Southern Hemisphere recommendation. And as all of you probably remember, we do a Southern Hemisphere recommendation because we have a couple of US manufacturers who are licensed to produce vaccine for the Southern Hemisphere. And so we meet in essentially the same format as we do this time of the year for the Northern Hemisphere, and they will make recommendations for strains to be included in those vaccines. But at this meeting, besides the review of the surveillance and the surveillance of virus strains and the availability candidate vaccine strains, we also had a special session entitled the challenges and opportunities presented by the disappearance of the B Yamagata's lineage of B Influenza. And so the committee did vote and the committee heard that at this meeting that changing the vaccine composition from a quadrivalent to a trivalent for the Southern Hemisphere 2024 would put at risk quite a few doses of quadrivalent vaccine that were destined for the rest of the world. So the committee did vote at this meeting unanimously to approve the recommendation for a quadrivalent vaccine for the Southern Hemisphere. But at this meeting, as I said, we had this discussion about the B. Yamagata lineage and what it might take to change the composition to a trivalent, and we also had a voting question, and the committee voted at this meeting unanimously to recommend excluding the B Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible. I will note that the committee members emphasized the importance of setting firm timelines for implementing the exclusion of the

Yamagata lineage antigen from quadrivalent influenza vaccines, and they wanted us to work toward a 2024/25 implementation date for the US vaccine in the Northern Hemisphere.

The next couple of slides, I'm going to talk about what's been going on in the last four and a half, five months. I'm not going to go over this slide, just briefly summarize the situation with B Yamagata viruses. I'm not going to go through all of this. We talked about it in October, but essentially, these are some of the highlights of the important points. Influenza B diverged into two antigenically distinct lineages in the 1980s. In fact, Yamagata viruses emerged from a B Victoria like ancestral strain. Because of these two antigenically distinct lineages, there was an effort to make quadrivalent vaccines that contained antigens from both lineages. These quadrivalent vaccines began to be licensed in 2012, and the idea was to try to avoid a mismatch of the B Yam component of the vaccine, and these were fairly successful. But as I said, now we're in March 2024, and there have been no confirmed detections of circulating B Yamagata lineages viruses basically, four years now. The right just shows a little tree that we put together. And I want to thank my colleague in the division of viral products, Gabriel Pera, who will prepare this, and it shows some of the how the viruses B Yamagata viruses diverge. I also want to point out that the B viruses, these are lineages, these are not clades, and although they're antigenically distinct, they're not as distinct as, say, H1 from H3.

The next slide briefly outlines some of the steps that we have taken after this VRBPAC meeting to try to affect the removal of the B Yamagata component from the vaccine. As we noted in that meeting on October 5th, 2023, there are regulatory and manufacturing challenges to reverting from a quadrivalent vaccine that contains an H1 and H3, a B VIC and a B Yam component to a trivalent with an H1 and an H3 a B VIC component. We noted at that time that these challenges differ in different parts of the world and trying to affect the global coordinated change would be difficult because of the different regulatory requirements, different manufacturing aspects. But in the United States, the challenge is to attract to reverting to a trivalent formulation appeared manageable even for 2024/25. And since that VRBPAC meeting in October, the FDA has engaged with all US Influenza vaccine manufacturers, both together

separately and I'll note, actually, multiple times in an effort to identify the necessary steps for a trivalent formulation transition for the next Northern Hemisphere influenza season.

At this point in time, each of the US influenza vaccine manufacturers have submitted updated regulatory files related to a trivalent influenza vaccine. And approval of all the necessary regulatory submissions is on track for a 2024/25 PIV implementation for all licensed U.S. influenza vaccine manufacturers. But because quadrivalent influenza vaccines will still be distributed in other parts of the world, some U.S. influenza vaccine manufacturers will continue to manufacture both TIV and QIV for 2024/25. However, the TIV and the QIV will be licensed for such manufacturers, but only trivalent vaccine will be distributed in the United States. I'll note in the next slide, I'll talk about the most recent WHO recommendations, but when they came out with their recommendations of a couple of weeks ago, they also reiterated their earlier recommendations concerning the exclusion of BE Yamagata strain component.

So this is the most recent recommendation from WHO. The WHO made their Northern Hemisphere recommendation on February 23rd, 2024, and their recommendation was that for trivalent vaccines for use in the 2024, 25 Northern Hemisphere influenza season. They recommended the following for egg-based vaccines. They recommended an a Victoria 4897 2022 H1N1 PEDMO 9 like virus. A TYN8 2022 H3N2 like virus and a B Austria 1359417 2021 B Victoria Lineage Virus. For cell culture, recombinant based vaccines, they recommended an Avis, Wisconsin 67 2022 H1N1 PDM 09 like virus in 80 Massachusetts 18 2022 H3N2 like virus and also a B Austria 1359417 2021 B Victoria lineage virus. The WHO at this meeting on February again noted that there are no confirmed cases of B Yamagata lineage viruses after March 2024 and they reaffirmed their previous opinion that the B Yamagata lineage antigen should be excluded from influenza vaccines that is no longer warranted. However where quadrivalent vaccines are still used, the B Yamagata lineage component remains unchanged from previous recommendations, and this is again a B Phuket 3073 2013 B Yamagata lineage like virus. So you'll hear a

report from the WHO as well as US surveillance, as I noted, and then we will proceed with a discussion and voting questions, which I think are on the next slide.

These will be the voting questions that we will come back to after all of the discussions today. I've divided it into three questions. The first one is, does the committee recommend a trivalent 2024, 25 formulation for egg-based influenza vaccines in the US that contained the following virus strains. The same ones on the previous slide and A Victoria 4897 2022 H1N1 PDM 09 like virus and a Thailand 8 2022 H3N2 like virus, and a B Austria 1359417 2021 B Victoria lineage like virus.

The second question will be for cell and recombinant based vaccines. Again, does the committee recommend a trivalent 2024, 25 formulation for cell and recombinant based influenza vaccines in the U. S. that contain the following virus strains? An A Wisconsin 67, 2022 H1N1 PDM 09 like virus and a Massachusetts 18 2022 H3N2 like virus and a B Austria 1359417 2021 B Victoria lineage virus.

The third question we will pose to the committee is for US licensed quadrivalent influenza vaccines intended for ex US Distribution. Does the committee recommend the inclusion of a B Phuket 3073 2013 B Yamagata lineage like virus? That's the second influence of B strain in the vaccine. So I hope I've explained that clearly enough, but I'm happy to take questions if not. Over.

Dr. El Sahly: Thank you, Dr. Weir. I would like to invite the committee members to use their raise your hand function should they have a question to Dr. Weir. And the first question comes from Dr. Bernstein. Dr. Bernstein.

Dr. Bernstein: Always clear what you're suggesting. I just had a question and maybe I should wait until colleagues from the WHO speak, but when I looked at the WHO FluNet surveillance data for 2017 to 2022, 15 to 18 percent of the Influenza B lineage was not determined. And then when you look at the currencies in about half or more of the influenza B are listed as lineage is not determined, what does that mean? Or do we know why that is the case?

Dr. Weir: Yes, and you're right. Dr. Kondor will talk about this when she gives her presentation. There's always a large number of influenza viruses, both A and B, that are not specifically typed. My understanding is that over the last couple of years, there's been an effort to type more and more of the influenza Bs for the very reason that you're alluding to, is that are we really getting a good picture of what the Influenza B Victoria versus Yamagata, but I know Dr. Kondor will cover this when she gives her talk. But again, there's always a large number that are not typed. It's just the way the typing does. But again, I think a lot more is being effort is being put into this than even a few years ago.

Dr. Bernstein: Thank you.

Dr. El Sahly: Unless the ones that are yama, gata have particular characteristics that makes them not typeable, you would expect those that didn't get typed to be proportional to the one that did get typed. Do we know?

Dr. Weir: Yeah. Again I know she will cover this when she talks, but I think that is the assumption that the percentage representation you get when you type would reflect what's not being typed. Yes, that would be my understanding.

Dr. El Sahly: Thank you. Any other questions from the committee? I have a question, which is pertaining to the last voting question, for the ex US recommendation to maintain the quadrivalent for valid reasons. However, my question is are the wheels in motion also internationally to move to trivalent given the lack of circulation? Do we know that?

Dr. Weir: The WHO has been pretty clear in their recommendations. And we've had meetings with other regulators and other public health authorities over the last year. It's pretty clear that everyone will move in this direction, and I think you'll hear the same thing when the manufacturers give their report. It's just that as we talked about in October, there are different requirements in different places, and I hate to say it was easier in the US, but it probably was a little easier in the US. Every manufacturer already had a trivalent license. They were all licensed, originally it is trivalent, in some parts of the world, there was never a

trivalent license. So that takes a little bit of time. But I think the short answer to your question is yes, it is moving in this direction everywhere.

Dr. Weir: Great.

Dr. El Sahly: Thank you. Any other questions? I see no raised hands. Thank you, Dr. Weir. Our next speaker will be Dr. Lisa Grohskopf. Dr. Lisa Grohskopf will give the US surveillance for the influenza in the past season. Dr. Lisa Grohskopf is the medical officer epidemiology and prevention branch at the influenza division of the Centers for Disease Control and Prevention. Dr. Groskopf.

U.S. Surveillance: Lisa Grohskopf, M.D., M.P.H.

Dr. Grohskopf: Good morning, thanks again for the opportunity to be here with you today. This is going to be a brief summary both of the '23/'24 US influenza activity thus far this season and preliminary vaccine effectiveness estimates from four CDCVE networks for this season. We're going to start first with surveillance and in that we're going to first, cover logic surveillance. These charts summarize information concerning influenza test results reported weekly to CDC from participating clinical laboratories on the left and public health laboratories on the right. In both of these charts and in the rest that follows, surveillance week is on the X axis. The material I'm going to present in this and in the remaining surveillance slides is from the most recent FluView report, which is for surveillance week 8, that's the week ending February 24th, 2024. There's a link to FluView in each of the surveillance slides for those who wish to seek more information. On the left from the clinical labs, what we're going to focus on is the left side Y axis, which is the percent of specimens that were positive for influenza and which is represented in the body of the chart by the solid black line. The percent of specimens that are positive for flu is one of the indexes we used to gauge flu activity over the course of the season. For the week ending February 24th, 14.2 percent of specimens were positive. The peak of the percent positive specimens had been 18.1 percent occurring at week 52, that's the end of December. On the right side from the public health labs, we're going to focus on the colored bars, which denote the relative types and subtypes of influenza viruses associated with these positive test results.

Overall, this season, Influenza A H1 PDM 09 viruses have predominated with co circulation of influenza age 3 and 2, which are represented in red and be in green, the PDM 09 viruses are in orange. In recent weeks, if you look at the relative color makeup of the bars, the proportion of H3N2 and B viruses compared with the H1N1 PDM 09s has increased somewhat.

Next, we're going to move on to influenza like illness or ILI surveillance. This is from ILINET. In this network, and in much of the literature that's similar, this is defined as respiratory illnesses that includes fever plus cough or sore throat. Again, these are from which is a large network of providers, which report weekly the percent of outpatient visits that were for influenza like illness. So these illnesses here do not represent influenza. Specifically, they're not lab confirmed illnesses. However, tracking activity during the season provides some sense of potential flu activity. Several seasons are shown here for comparison, and the current ‘23/‘24 season is the red line with the superimposed dots. Nationwide during week eight again, this is the weekend in February 24th, 4.4 percent of outpatient visits in this network were reported to be due to ILI. This is down from a peak of approximately 6.9 percent during week 52.

These are data from FluserveNet, which monitors lab confirmed influenza hospitalizations. This graph shows cumulative hospitalizations per 100,000 by week for several selected seasons with the current ’23/‘24 season represented by the red line with the superimposed dots. Each of the seasons is represented by a different color. These data are updated as more information becomes available. You'll see that the red line does extend to week eight, but it's, dotted there, those periods of time are a bit more preliminary than the earlier periods of time. As of February 24th, overall cumulative hospitalization rate was 61.5 per 100,000, and you can see that rate approaches last season in the green line, the darker green line, which plateaued at around 61, 62 per 100,000, although you see that the line for this current season is shifted a bit later in the season. We had somewhat more early onset season last year. Right now, we're at about 100,000. The highest cumulative hospital rate, it's not shown here, was among adults 65 and older

at 166.1 per 100,000, followed by those 50 through 64 years at 74.8 per 100,000 and children 0.4 years at 63.6 per 100, 000.

The last 2 slides for surveillance are both mortality data. First, this is pneumonia and influenza, or PNI mortality surveillance from the National Center for Health Statistics mortality surveillance system. These data come from diagnoses reported on death certificates. So this does not represent lab confirmed influenza illness. As of February 29th, 2024, 0.7 percent of deaths that occurred during the week ending February 24th, 2024 were due to PNI. This is a down from a peak of 1.3 percent during week one of the year.

And this is our last surveillance data slide. This is pediatric mortality influence associated confirmed influence associated. Pediatric deaths have been reportable in the US since 2004. we have a number of seasons represented here starting from 2020/‘21. As of the weekend in February 24th, 93 pediatric deaths have been reported.

In summary, as of the weekend in February 24th, 2024, US influenza activity has lessened slightly in recent weeks, but is currently still ongoing. The percent of positive tests peaked at about 18 percent in late December and is currently about 14 percent. Flu A H1 PDM 09 viruses have predominated with co circulation of flu A NB viruses, flu A H3N2 and B viruses. The cumulative influence associated hospitalization rate is currently 61.5 for 100,000, and 93 influenza associated pediatric deaths have been reported thus far this season.

So now we're going to move on to interim estimates of ‘23/‘24 seasonal influenza vaccine effectiveness. These are results that were discussed at the ACIP meeting last week, the February 2024 meeting. They were originally presented by Dr. Aaron Frutos and I'm really grateful to him and the rest of the team for these slides and for all of this work. I'm also a summary of the results that I'm about to present was also published in morbidity and mortality weekly report on the 29th of February.

These estimates come from four CDC networks, which, when taken together, evaluate influenza vaccine effectiveness across age groups, some six months and older and up. So it's children, adolescents and adults in both inpatients and outpatient settings. Before summarizing the results, we're going to take a moment just to describe the networks and their components and their methods.

Here are the four networks and the age groups they focus on and the outcomes. The investigating respiratory viruses in the acutely ill network evaluates adults aged 18 years and older and influenza associated hospitalizations VE against hospitalizations. The new Vaccine Surveillance Network, or NVSN, evaluates children and adolescents six months through 17 years and examines VE against outpatient visits, emergency department, and urgent care visits and hospitalization. The US Flu Vaccine Effectiveness, or US flu VE network, evaluates children and adolescents, 6 months through 17 years and adults, 18 years and older and evaluates VE against outpatient visits, emergency department and urgent care visits. And finally, the virtual SARS CoV2 influenza and other respiratory viruses network revision looks at children and adolescents, 6 months through 17 years and adults, 18 years and older and evaluates VE against emergency department and urgent care visits and hospitalizations.

So, this figure just summarizes the geographic distribution of the sites, participating in each of the networks by state. Taken together, the CDC flu VE networks evaluate patients from 22 states.

A little bit on the methods. There are a lot of similarities among the methods in these four networks. In each, the enrollees have acute respiratory illness, everybody presents to a health care setting with an acute respiratory illness. The results here, the dates vary slightly between the networks, but overall they represent data collected from fall 2023 through early 2024. All foreign networks use a test negative case control design, which involves comparing vaccination odds among case patients who test positive for influenza with control patients who test negative for influenza, and this is done by molecular assay. Vaccination status is defined by receipt of any ’23/‘24 seasonal flu vaccine, according to medical records, immunization registries claims data and or self report.

In all analyses, VE is calculated as one minus the adjusted odds ratio times 100percent. As far as adjustments, adjustment occurs in all the networks for geographic region, age, and calendar time of illness. For IV, the US Flu VE network and vision, it's also adjusted for sex and race and ethnicity. For US flu VE network, it's also adjusted for days between illness onset and enrollment and for self-reported general health status. VE estimates were calculated for Influenza A subtypes, when possible; however, this isn't always possible due to small numbers, also, it should be noted that subtype information for the flu viruses is not available for vision. You'll see in some of these slides that VE was not estimated for some age groups and settings when sample size was small, or when the models did not converge.

So, we're going to go over results by age group. We're going to start out with the pediatric population, age 6 months through 17 years. Before we launch into the results, just want to orient you to the format of the slides that follow. In the first column, we have the listing of the relevant networks and specification of whether the results are inpatient or outpatient for that particular line. The middle two columns show the numbers vaccinated over the total denominator divided by case, that's flu positive versus control or flu negative status. And the last column shows the estimated adjusted VE and the 95 percent confidence interval for each estimate. Looking at results for pediatric patients, VE estimates are available from NVSN, US flu VE, and Vision for Outpatients, and NVSN and Vision for Inpatients. For all flu A and B, outpatient VE was 59 percent in NBSN, 67 percent in flu VE, and 60 percent in vision. Inpatient VE was 61 percent in NBSN and 52 percent in vision. All of these results were statistically significant. That is, you can see that the confidence interval does not cross 0.

We're going to look next at Influenza A viruses. So this is all flu A, not subtype specific for this first one. Outpatient VE was 55percent for NVSN, 46percent in US Flu VE and 59percent in vision. And for inpatients it was 56percent in NVSN and 46percent in vision. All of these results were statistically significant. We have some subtype specific data next. First with a H1N1 PDM 09. For these viruses, outpatient VE was 54percent in NVSN and 61percent in vision. We have one estimate for NVSN for inpatients, and that's 60percent. All of these results are statistically significant. For flu A H3N2 viruses,

we have somewhat smaller numbers here, so you're going to see we have a couple that are listed as not estimated due to small numbers. Outpatient VE was 55percent in NVSN and was statistically significant. And outpatient, VE and US flu VE network and Inpatient VE and NVSN were not estimated due to small numbers.

And finally, for the pediatric results, pediatric VE against influenza B, outpatient VE 64percent in NVSN, 89percent in US Flu VE and 79percent in vision. All of these were statistically significant. Inpatient VE and NVSN and vision were not estimated due to small numbers. So now we're going to move on to the full adult population aged 18 years and older. For adults aged 18 years and older, the estimates are available from US flu VE and vision for outpatients and for IV in vision for inpatients. We're going to start again with all flu A and B. Outpatient VE was 33 percent in US flu and 49 percent envision. inpatient fee was 44 percent in IV. And 41 percent envision. All of these results were statistically significant.

Looking at flu A viruses, not subtype specific, outpatient VE was 27 percent in US flu and 46 percent in vision. Inpatient was 42 percent in IV and 40 percent envision. All of these were statistically significant. For subtype specific results for H1N1 PDM 09 viruses. Outpatient fee was 25 percent in US flu VE and inpatient VE was 50 percent in IV. Both of these results were statistically significant.

For H3N2 viruses, outpatient VE 54 percent in US flu VE and was statistically significant. Inpatient for Ivy was not estimated due to small numbers. And for adult VE against flu B, outpatient VE 78 percent in both U. S. flu and vision. Inpatient VE 60 percent in vision. All of these results are statistically significant. Inpatient for IV could not be estimated due to small numbers.

Okay, so the last couple of sets of slides are subgroups of the adult age group. We're going to start with adults age 18 through 64 years. For this age group, for all flu A and B, outpatient VE was 25 percent in US flu VE and 52 percent in vision. Inpatient VE 49 percent and IV and 40 percent envision all of these results are statistically significant. The VE estimate for this age group that is 18 through 64 years in the

US flu VE network is somewhat lower than the other estimates. For flu A outpatient VE was 13percent in US flu VE and 49 percent in vision. Inpatient VE 42 percent in IV, and 38 percent in vision. All of these are statistically significant with the exception of the US flu VE estimate for which the point estimate is also lower compared with the others. For Influenza B viruses, outpatient VE 75 percent in flu VE and 79 percent in vision. Inpatient 50 percent in vision. In contrast for what we saw for the flu a viruses for the B viruses. We see somewhat more consistent estimates among the outpatients for VE estimates. Inpatient VE for IV was not estimated due to small numbers.

Last age group is adults aged 65 years and older. For this age group, there are estimates from flu VE network and vision for outpatients and IV and invision for inpatients. For all flu A and B for outpatients estimated VE was 51 percent for flu network and 41 percent for vision for inpatients, 42 percent for both IV invision. All of these results are statistically significant. For flu A, all flu A, for outpatients VE estimated 52 percent for US flu and 40 percent for vision. For inpatients, 47 percent from and 42 percent from vision, all of which are statistically significant. For flu B viruses, data were sufficient only for an outpatient estimate from vision, which was 69 percent and statistically significant.

Lastly, we're going to just go over a brief summary of these results for VE. In summary, and these preliminary estimates from four CDC VE networks vaccination with a ’23/‘24 influenza vaccine, reduce the risk for medically attended outpatient visits and hospitalizations among children, adolescent, and adults across 22 states. Vaccination was effective against both influence a mostly subtype H1N1 PDM 09 , and B lineage Victoria viruses as circulated the season results are relatively consistent across networks.

That's all I have to present for you today. I'd like to thank the CDC influenza division at the prevention branch surveillance team and influenza prevention and control teams for all the work and getting the data that is put together every year for these slides and also the many surveillance network contributors and collaborators from CDC, IV, NVSN, the US Flu VE network and vision. Thanks very much. I'd be happy to take questions.

Dr. El Sahly: Thank you so much, Dr. Lisa Grohskopf. I invite my colleagues to use the raise your hand function so we can begin the Q and A session beginning with Dr. Offit.

Dr. Offit: Yes, thank you Lisa for that clear presentation. My question to you is I'm trying to get a better sense of exactly who is hospitalized, goes to the intensive care unit, and die from influenza. Is it published extensively on how those groups fall out for code? Are there any critical differences between flu and COVID and who is most likely to be hospitalized and die, or not?

Dr. Grohskopf: There is a lot of overlap in the risk factors as far as they've been at least elucidated so far in terms of who is more likely to get more severely ill and who's likely to be hospitalized. I think it's overall a little difficult to draw comparisons just on that basis, since there might be also some differences in testing practices between the two. It's possible that those might change over time. But I don't think it's really possible to elucidate at this point, major differences between the two, a lot of the risk factors do overlap.

Dr. Offit: Just one quick follow-up question. If I might, the most countries regarding their coven recommendations will focus on high risk groups. We don't but nor does Canada, but arguably we could. I'm trying to understand would it make sense to focus on high risk groups when we make a flu recommendation or is there a reason why I say some countries recommend a flu vaccine for all over six months of age, but at the same time target high risk groups for code?

Dr. Grohskopf: When you speak of targeting risk groups, you mean for vaccination or for non-pharmaceutical, non-medical? For vaccination, ACIP recommendations we do note that there are individuals at higher risk for flu. Some of those are age based. Some of those are chronic illness based and there is, there is a listing for priority groups, for example, for situations where there's a shortage of vaccine and those groups are called out there. We also, in a lot of our other literature, for example, web pages do point out that flu vaccination is important for everybody, but particularly important for some people. The difficulty with focusing only on individuals who are considered in a high risk group for

vaccination is that we do see that even if you don't have any risk factors, we can't really predict who's going to get very sick, or who's going to die in, for example, in the pediatric literature that some of our group has published in some cases among the individuals who end up getting hospitalized, half of them didn't have other than their age and risk factor, other than the age-based one. So that is the underlying reason why the recommendations are written the way they are currently.

Dr. Offit: Thank you, Lisa.

Dr. Grohskopf: Sure.

Dr. El Sahly: Dr. Chatterjee?

Dr. Chatterjee: Yes. Thank you. I have two questions. The first one is whether there are any data on the timing of vaccination relative to the positive tests. I.e., was their sufficient time to develop immunity.

Dr. Grohskopf: That's a really good question. In general, within the networks the vaccine must have been received within two weeks or more before the illness onset.

Dr. Chatterjee: Okay. So that is taking into account. And then my second question is about any difference in VE based on the vaccine type. Live attenuated versus the other injectable vaccines or among the various vaccines that are given, is that data captured anywhere?

Dr. Grohskopf: Vaccine type is captured, it usually, in general, at this point of the year, there's two issues that affect ability to determine vaccine type. Generally, in February, what we have are preliminary estimates and one of the things that happens over the course of time between now and the fall is confirmation of vaccination status and to the best extent possible. What brand was received at this point? And we still have some that are self report. And it takes a little time to confirm that the other issue generally has been, going back many years now that sometimes we simply don't have enough occurrences of a specific vaccine type to be able to make an estimate. This is a particular issue as a lot of LAIV with either hasn't been as much LAIV use in the network. There were times in the past where we were able to

make estimates for LAIV specifically, and even a couple of seasons where it was possible to make an estimate for high dose specifically, but it remains to be seen whether that's going to be possible this season. And generally, it's not something we have for preliminary estimates at this time of year.

Dr. Chatterjee: Thank you very much.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah, I just have, I have just a clarifying question, but not a question of comment maybe. When we think about the COVID 19 vaccines or the SARS COVID 2 vaccines, it's pretty clear that the vaccine efficacy may be listed as lower than it really is because everybody's been infected or vaccinated already. And I assume the same thing's true for flu that you have efficacies of 50 percent of 40 percent or 60 percent because the underlying population except perhaps for very young children have all been infected or vaccinated already so that the vaccine efficacy might actually be much higher if it was compared to a naive population. Is that fair do you think?

Dr. Grohskopf: That's something that's been discussed increasingly in, in recent years. And actually in recent months we do generally see the higher be in young children. And some of that may also be because of their immune system. So some of it, it's a little bit difficult to tease out, I think, mainly because with flu we do have three different, generally, a number of different viruses co circulating every year. VE tends to vary with subtypes. We also have the issue of match every year. So there are all of those other things that are conflating this entire picture. But that's an argument that has been made. Yes.

Dr. El Sahly: Dr. Janes.

Dr. Janes: Thanks, Lisa. I wanted to follow up on one of the lines of questioning that was raised with Dr. Weir around the extent to which we're subtyping and determining lineage for these viruses as it relates both to profiling the surveillance data and the VE estimates. Can you characterize whether we're increasing our characterization of these viruses over time whether things are improving with regard to the proportion of viruses that are subtyped and lineage determined.

Dr. Grohskopf: I don't really know the answer to that question off the top of my head. If we're talking about surveillance data versus, study data, flu B network data I can. I can track that down and get back at later in the session if you like. And also at least with regard to surveillance as possible and my colleagues that's going to present later might have some idea.

Dr. Janes: Thank you

Dr. Grohskopf: In general, one thing to note, though, is that I'm just looking at the surveillance data for the clinical laboratories. We generally do not have and that's why the graph is the way it is. It basically just is broken down into A viruses in yellow and B viruses and green. A lot of the clinical labs don't have subtyping data that's reported as opposed to the public health labs,

Dr. El Sahly: I have a couple of questions. What was the vaccine coverage this year? Did we see any trend differences in vaccine coverage compared to previous years? Are we still good at high older adults in 60 percent and younger adults, slightly lower?

Dr. Grohskopf: Overall, unfortunately, vaccine coverage has dropped at least a few percentage points among all the age groups. If you look at compared with two seasons ago we've had some step wise drops. Even among those 65 and older, which, generally they're the group in which we see the highest coverage and still are the group in which we see the highest coverage, but we've had a bit of a stepwise decrease in coverage over the last two seasons from ’21/‘22 to now.

Dr. El Sahly: The other question I have is any ideas as to the reason, or is that still under investigation? I don't know.

Dr. Grohskopf: Within the coverage networks, we have a number, but we don't always know why difficult to say. One thing that's been put forward is the fatigue at vaccine messaging. Because there has been quite a little bit of promotion of vaccines that we have now, not just flu, but COVID-19 vaccine and then this year vaccine was introduced. It is also conceivable that, again, we don't know this, but it's conceivable that there might be some confusion among people with regard to timing. Can I get them all at

once? Do I have to get them all at once? If I spread them out, do I not have enough time to get them? There are any number of possibilities, but I don't think we know the reason.

Dr. El Sahly: I hope the trend doesn't continue, especially among the old. The other question I have is does the Flu VE network that was the one on the first line in your tables, it seemed to always be well, not always in many of the slides. It was a bit of an outlier. They have different methodology that compared to others. They had some of the lower estimates.

Dr. Grohskopf: It seems particularly driven at least this year by the 18 through 64. The sort of younger adults, as opposed to the older adults and mainly by H1N1 PDM 09, H3N2, sorry, the other estimates are somewhat more consistent. We do sometimes include the VE network. There have been some previous seasons where we've seen one age group that was a bit of an outlier. We don't know the reasons for this yet. One thing I just want to mention is, again, these are preliminary estimates and there will be more information and analysis ongoing as the season progresses. I don't have an explanation for that, at least now.

Dr. El Sahly: Okay. All right. Thank you so much Dr. Grohskopf. I don't see any more raised hands, but there'll be opportunities to ask additional questions in the discussion period of the meeting.

Next, Dr. Rebecca Kondor will go over the Global Influenza Surveillance and Characterization. Dr. Rebecca Kondor is the Interim Director of the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza at the NCIRD Influenza Division, Virology, Surveillance and Diagnosis Branch, CDC. Dr. Kondor.

Global Influenza Virus Surveillance and Characterization: Rebecca G. Kondor, Ph.D.

Dr. Kondor: Thank you very much for the opportunity to present today. And this is my first VRBPAC.,Ss I'm very excited to be part of the discussion later as well. I have the pleasure of going over the global influenza virus surveillance and characterization data that led to the WHO vaccine recommendations last month, as Jerry has already outlined.

Okay, so in this presentation, I'll give an overview of the influenza vaccine selection process and more information about the WHO information meeting that was held last month. As Dr. Weir mentioned, there were changes in the recommendations compared to last season's vaccine composition. Specifically, when we look at the vaccine antigens recommended, the A H1N1 PDM09 and the B Victoria and B Yamagata lineage vaccine antigens remained unchanged. However, the A H3N2 vaccine antigen was updated compared to the Northern Hemisphere vaccine composition that was given this season. And this is the same virus that was recommended in September for the 2024 Southern Hemisphere vaccine.

The consultation meeting was held February 19th, the 22nd in Montrose, Switzerland, and the majority of information that's presented at the consultation meeting is a large collaborative body of work from the Global Influenza Surveillance and Response System. This includes coordination by the Global Influenza Program at the characterization for antigenic and genetic data from the WHO Collaborating Centers, the large amount of testing and analyzing and shipment of specimens into CCs from our National Influenza Centers, our collaborations with our Central Regulatory Laboratories, And our age five reference laboratories. So, a lot of data is presented at this meeting and I just want to first of all, thank and acknowledge all of the hard work from these individuals. So this was our first in person meeting since the pandemic and in this meeting, we discussed not only the recommendations for the vaccine composition for our seasonal or epidemic influenza viruses. But also proposed a new candidate vaccine virus development for zoonotic influenza. The consultation was chaired by Dr. Diane Wong, the director of the WHO Collaborating Center in Beijing, China, and cochaired by Dr. Kanta Subbarao, the director of the WHO Collaborating Center in Melbourne, Australia. This was actually Kanta’s last vaccine consultation meeting because she is planning to step down in the next couple of months.

In addition to the cochairs, there were 10 advisors, which consisted of directors of WTO collaborating centers and the essential regulatory laboratories and disclosures, but interests were given at the meeting. In addition to the advisors, there were 32 observers from national influenza centers,

collaborating centers, ERLs, H5 reference labs, as well as both national and regional public health agencies and academia. And then with our zoonotic, we have partnerships with WOA, FAO, and Oflu.

Okay, so this slide gives a large overview of the types of data that are used during the vaccine consultation meeting to address whether or not a vaccine update is needed. This includes epidemiologic and clinical data. Asking where the recent epidemics occurring, and are they unusual in their magnitude or disease profile? As I mentioned, a lot of virus surveillance from our national influenza centers, part of GISRS are conducted year round. And the information is cumulative for the four different virus groups. And then from this subset of testing, viruses specimens are sent to WHO Collaborating Centers for further characterization. Includes genetic sequence analysis primarily focusing on the HA and NA gene evolution, but also looking at the genome constellation for reassortment or other patterns of evolution. Antigenic characterization of a representative set of viruses are performed. In this, we look at a couple of different models. The main model being a naive animal model using host infection ferret antiserum to look for antigenic variation. And we also look at human serologic data from post vaccination with this current season. We also bring in data from the vaccine effectiveness studies from the global consortium. And as important, this global data set requires a lot of data integration to compare results across the WHO Collaborating Centers in terms of not only results, but methods, regions, and viruses.

And lastly, is the question of looking at the available candidate vaccine viruses for each subtype and comparing their characteristics. Some of the main questions that I'll go over in what led to the committee's decision are really asking whether the virus antigens will elicit immunity for each of the subtype that we discussed against the diverging or diverse amount of viruses that are circulating for that particular subtype. And when we're choosing an antigen, we really want an antigen that confers a breadth of immunity across the genetic diversity of the viruses circulating. So examples of this in terms of the data is looking at the significant epidemics and then within each type and subtype, we're looking at the genetic information where there might be regional differences in circulation. We're also looking to understand where are the changes that are occurring within these viruses in particular antigenic sites in the

hemagglutinin and neuraminidase. And then how is this spread, where are these particular viruses circulating? And looking at the antigenic distinction, comparing ferret antisera with our current vaccine reference viruses to see how well these ferret antisera recognize these new emerging genetic variants. And then proportionality, so understanding what particular genetic variants may be increasing or decreasing over time.

And then lastly, getting that human post vaccination data to understand how well the current vaccines induce antibodies against the cocirculating or emerging genetic variants that we've detected and then looking at that breadth of potential, recognition of a new vaccine antigen. Will it recognize a very specific group within its subclade or does it have a breadth of protection across the genetic diversity of that particular subtype? As already presented, these are the vaccine recommendations for the Northern Hemisphere 2024/2025 season. For egg-based vaccines, as said previously, the H1N1 component remains A Victoria 4897 2022, the H3N2 component is updated to a Thailand 8 2022, and the B Victoria lineage remains B Austria 1359417 2021.

For Cela recombinant based vaccines, the H1N1 component remains A Wisconsin 67 2022. The H3N2 component, again, is updated to A Massachusetts 18 2022, and the B Austria remains the vaccine recommendation for the B Victoria lineage for quadrivalent vaccines. The above three components plus the B Phuket, B Yamagata like antigen is recommended and the link to that recommendation can be found in the slide. Also this page shows other links to other documents from the consultation that includes the recommendation in FAQ, as well as a full list of available candidate vaccine viruses and reagents and guidance for tropical and subtropical countries. And as mentioned part of the consultation discussed the zoonotic influenza virus summaries and proposed new candidate vaccine development and a link to those recommendations and the candidate vaccine viruses can be found here.

This map shows the global viruses, which were shared from national influenza centers into the WHO collaborating centers and through the time period of September 1st, 2023 to January 31st, 2024 in terms of collection. We can see a large amount of influenza viruses from several countries across all

regions were shared with WHO Collaborating Centers during this time period. This data looks at summary data of type and subtype reported to FluNet from the global influenza surveillance and response system, and this hopefully will help answer some of the questions about the level of blue A subtyping and B lineage testing when we look at our northern hemisphere on the left and I boxed the time period that we'll be speaking to in this presentation, September through January, we can see in the dark blue green, these are the influenza A viruses reported. And we can see, then, the proportion that were subtyped as influenza H1N1 PDM09 or H3N2. And shades of orange are influenza B or influenza B Victoria, in the lighter orange. And what we can see here is that there are a significant number of viruses that don't have a subtype or lineage reported to FluNet. That is because of the overlaying types of surveillance information that is reported into FluNet and the timing of the information for a particular specimen when it's reported. As Dr. Grohskopf mentioned, in the United States, we have a large clinical laboratory network that, that performs panel of respiratory testing and which includes only typing influenza A and B. From this surveillance source, we're getting a large number of detections of influenza and the information of which particular type is present and circulating. However, we are not necessarily getting the subtype information from that particular surveillance network. So instead, in the United States, we have a layered approach. With virologic surveillance being coordinated by APHL in our influenza state public health laboratories that perform subtyping on a subset of influenza positive specimens. And we may have heard it before, but in this program, we have what's called rightsizing. This is asking the question of how many viruses do we need to subtype each week to have some level of confidence that we can detect a variant with greater than one percent and this is how we power to understand the predominant influenza A subtype and B lineage that is in the United States. So the proportion of information that's typed or subtyped that's reported to FluNet is really dependent on the underlying surveillance networks within a country. Some countries only have sentinel surveillance. So they're only testing a very small number of positive specimens in their network. And with our support from the WHO Collaborating Center at CDC, we've created and provide influenza A subtyping and B lineage assays for these national influenza centers. So the total number of influenza centers that are performing subtyping and B lineage typing has grown over the last couple of

years, but depending on where the epidemic is occurring, you're going to see different ratios of that information.

For example, if we look in the southern hemisphere, we can see that during September to January, there was still detection, although lower than when they had their peak activity during the May to July, but a cocirculation of both flu A and flu B, and for the flu As, the majority of viruses here were H3N2. To recap, in the Northern Hemisphere, we saw cocirculation of influenza A and B. For the influenza A viruses, we really saw differences in the subtype that was predominant in different regions, and we'll go through that when we go to the rest of the data. But both H1N1 predominated in some parts of the world, while H3N2 predominated in others. Throughout all of this was continual detection of influenza B, and where subtyping B lineage was performed, B Victoria viruses were only detected. Now I'm going to present the data for H1N1 PDM09 viruses during this reporting period. This graph shows the number of H1N1 PDM 09 viruses detected by GISRS for the years 2021 through 2024. Now, 2021 is this light blue line that you'll see barely above the increases on the Y axis. So we had, again, very little circulation of influenza H1N1 during 2021, and the reemergence of it in 2022, showing near the end of the calendar year of 2022, increased detections in the GISRS network. So the previous season, we can see that for H1N1 PDM 09, although there was a little bit of detections in the early January of 2023, we saw a much higher proportion later in the calendar year. And this was due to circulation in parts of Europe, and then the beginning circulation of the Southern Hemisphere. The Southern Hemisphere was predominantly H1N1, but co circulation of B Victoria and H3N2. And as you can see, beginning in week 40, a large increase in the yellow line, showing the increased activity of H1N1 during the Northern Hemisphere season, peaking at the beginning of December. And as the red line starts to decrease in 2024, we're continuing to see the amount of H1N1 viruses detected through GISRS decreasing at this time. This map takes, again, the GISRS FluNet data, looking at the percent positivity due to H1N1. Where we can see in the northern hemisphere, there was larger amounts of positivity in the Americas, Central America, and some countries in South America. Europe had a lot of H1N1 activity, as well as parts of Northern Africa,

and then parts of Asia, both West and South. And Southeast Asia and East Asia also showed significant activity. And as mentioned, H1N1 was a predominant flu A virus for the Southern Hemisphere, and there was continual activity in some parts of the Southern Hemisphere during this time.

So this is a large phylogenetic map from our collaborators at the University of Cambridge, which shows the genetic changes in the viruses by collection. So phylogeography showing both the temporal changes and the geographic location of the viruses. So the map here colors the different regions and then each tick mark shown on the temporal heat map here will show you when it was collected, what we can perceive the transfer H1N1 over the last two seasons. In the previous presentations, you have heard the co circulation of the 5A1 and the 5A2 viruses of H1N1. Now, the 5A1 viruses have really stopped circulating or being detected in circulation since the beginning of 2023. And one of the interesting post-coronavirus pandemic in terms of the evolution was the emergence of the 5A2A subclade with from within the 5A2A clade. These particular viruses had several genetic changes in antigenic site SB and near the receptor binding pocket. So a lot of genetic changes occurred in the 5A2 viruses in this emerging 5A2A clade. And at the same time, another subclade emerged called the 5A2A1s that had additional changes, most notably in the CA part of the HA.

So what have we seen in 2023/2024 season? As I mentioned, the southern hemisphere saw H1N1 PDM 09 predominantly, and they saw many different cocirculating viruses within the 5A2A subclade, and including some viruses in the 5A2A1. When we look at what's happened in more recent months since September, we continue to detect differences in the viruses that circulate. Seeing many viruses from the 5A2A in different geographic regions, including Europe, Asia, North America, and South America, and continual detection in parts of Oceania.

We also see 5A2A1 cocirculating in Europe, Asia, and North America in more recent months. We can then look at this on a map, and looking at the change in clade proportions between two different reporting periods. On the left is February to August collection dates, and on the right is the current reporting period, September through January. And the trends that we saw here, we saw in North and South

America, a higher proportion of countries had 5A2A1 during that reporting period. And this trend continues seeing a lot of 5A2A1 in the US and Canada, as well as parts of the Caribbean and South America.

However, we're seeing a mixture in Europe with cocirculation of 5A2A and 5A2A1 in different proportions based on countries. In Africa, we also saw 5A2A, but some countries also saw 5A2A1. Asia saw mainly 5A2A, but there were some parts of East and Southeast Asia where 5A2A1 predominated.

So a little bit different history in terms of H1N1s, where we're seeing cocirculation of subclade. This is our phylogenetic tree from the CDC showing the HA gene of H1N1 PDM 09 really drilling into the types of genetic changes that we're seeing within the 5A2A and the 5A2A1s during this reporting period. As I mentioned 5A2A and 5A2A1s are genetically related sharing changes at positions 54, 86, 189, 224, excuse me, 259, and 308. And then the further evolution of 5A2A1s at changes at positions. 137, 142, 260, and 277 in the HA1. If we look at the 5A2A1s, the majority of 5A2A1s which circulated during this reporting period share an additional change position 216. And we are starting to see some subgroups emerge within the 5A2A1s with additional changes in the HA1. For the 5A2A subclades, many viruses seen in Oceania belong down near the base of the tree, with additional changes at positions 94 and 216 shared, but other small emerging subclades continue to circulate there. The rest of the 5A2As are shown above and you can see that they were circulating in Africa, Asia, North America, and more recently with Europe. And in this group, they share a change in the HA2, and there are some small changes of convergent evolution that we're seeing at positions 137. Many of the viruses share a change at position 120, and there are also some subgroups with additional changes at either 169 or 47 and 96. When we go to risk assessment of these new emerging genetic groups, what we're doing is sub selecting viruses to represent the genetic changes in our further analysis. You'll hear me talk a little bit more about these particular viruses that I have named here when we get to our additional antigenic analysis.

So these graphs show the last three seasons for the Northern Hemisphere and the amount of H1N1 PDM 09 viruses antigenically characterized. And the total number characterized really is dependent

on the seasonality of the predominance. Last season, in the United States, a lot of the Influenza A activity was actually H3N2, but in parts of Europe, they saw an amount of H1N1 in activity later. All reporting WHO Collaborating Centers had data from H1N1 PDM 09 viruses antigenically characterized during this reporting period. You can see our WHO collaborating center in VIDRAL, which had quite a large H1N1 activity during their season continued to see and analyze additional viruses during September through January. This is looking at the results of our ferret antisera. Again, we use post-infection ferret antisera using the prototypes to either the cell Wisconsin 67 2022 like or the egg, A Victoria 4897 2022 vaccine viruses. Both of them are from the 5A2A1 clade. And what we can see with this is that the vast majority of the H1N1 PDM 09 viruses tested showed good recognition with the ferret antisera raised to both the cell and the egg prototype of the vaccine for 5A2A1. We can then take a look at this data in antigenic cartography space to see the genetic relatedness that we can characterize by calling them either 5A2A or 5A2A1 and seeing where the particular viruses appear in antigenic space. In purple, you'll see the 5A2A1 viruses, and in pink, you'll see the 5A2A viruses. The ferret antisera really shows that these viruses are not only genetically related, but antigenically related. And you'll also see in larger circles are either our cell or our egg prototype for the different vaccines. And so you can see the 5A2A1 egg and cell prototypes are shown right here in the middle of the 5A2A1 antigenic space. This is true both data from our collaborating center as well as the collaborating center in London. And we can see huge antigenic differences in our ferret antisera data are looking at viruses from the 5A1 group, which as I mentioned, is no longer circulating. So one of the questions that we have with our ferret antisera is how well does that ferret antisera recognize the genetic diversity? And so we can draw a map draw a circle, a serum circle that shows a homologous titer that is within eightfold. So good recognition of a virus will fall within this serum circle. And as you can see, for both collaborating centers, the 5A2A and the 5A2A1 viruses, both fall within that serum circle for the vaccine prototypes.

So with ferret antisera, we're not seeing a big antigenic differences with the 5A2A and the 5A2A1 viruses tested. This is a composite data for our human serology studies. Looking at post vaccination

human sera and this is including countries of the US, China, Japan, and the UK, and for the US, we have panels across age groups from the very young, 6 to 35 months, all the way to greater than 65 and multiple vaccine platforms. So this is our non-inferiority analysis asking the question of whether or not the host GMT to the current vaccine virus has a good recognition of the genetic diversity across the recent viruses. So each of the different viruses listed here across in the columns represents a genetic change in the hemagglutinin that we wanted to see the breadth of coverage with post-vaccination sera. And when we see a check mark or with a light blue this means that the post GMTs to the vaccine are noninferior against the new genetic variant that we're testing. Where we're starting to see changes and in orange shows that the lower bound of the GMT ratio shows reductions against these particular genetic variants. If we look across the selected viruses from 5A2A1. For the most part, we see good recognition of the genetic variation. There were a couple of panels that did show a little bit of reduction. Where we did see a little bit more reduction was in the genetic variation of the 5A2A. And however, for the most part, there was good recognition for the majority of viruses tested.

We also have a summary for antiviral susceptibility specifically to neuraminidase inhibitors. Over 2000 viruses were analyzed and 22 showed evidence of reduced susceptibility to neuraminidases. And then with specific substitutions that have previously been shown to confer reduction by NAIs. We also have information on endonuclease inhibitors. 1,656 viruses were examined, and one had a substitution in the PA gene that showed reduced susceptibility to biloxivir or voxel.

In summary, the data presented supported keeping Wisconsin 67 2022 like and A Victoria 4897 2022 from the clade 5821 as a vaccine antigens for the 2024/2025 Northern Hemisphere season H1N1 PDM 09 viruses circulated globally and as I mentioned, predominated in most geographic regions. The phylogenetic tree showed cocirculation of 5A2A and 5A2A1, but regional differences in which clade predominated, when we looked across the genetic diversity using post-infection ferret antisera against the vaccine components, we saw good recognition of both 5A2A and 5A2A1 viruses. And this information was also seen when looking at post vaccination human sera showing our post vaccination geometric mean

titers were not reduced significantly across the selected viruses from the 5A2A and the 5A2A1 genetic diversity.

Now, moving on to the H3N2s. Again, a similar graph showing the reported amount of viruses detected that were A H3N2 by GISRS. And a little bit different where in 2021, we really didn't see any H1N1. At the end of 2021 we saw the reemergence of H3N2. This led to several detections throughout 2022 again peaking near the end of that calendar year. And if we look back at our 2023 season we can see significant activity during the Southern Hemisphere timing, as well as that large peak of activity that occurred in the northern hemisphere during November of 2023. And when we look at this, we can see a peak in November, but then more recent collection dates are actually decreasing for H3N2. Now that we see this at a global level of all reported data, let's look at where H3N2 viruses were more dominant compared to H1N1s. Here we can see a little bit of a regional difference in that the Americas actually had a quite low positivity for H3N2. Mainly influenza A H1N1 circulated here. There were countries in Europe that had more H3N2 than H1N1, and you can see a large amount of H3N2 activity in parts of Asia, South Asia, in China, as well as Southeast Asia and parts of Oceania during this time. In Africa, there were several countries that actually had increased H3N2 activity as well. Here we have a little bit of difference between H1N1 that the large amount of activity for H3N2, especially in China during this time period.

Again, a similar phylogeography map for H3N2s. We've introduced before the different subclade nomenclatures. And what is interesting for influenza, we had several subclades cocirculate post COVID-19 pandemic with the reemergence of influenza. We had two main clades, clade 1 and clade 2. Clade 1 was predominantly detected in China, and this clade has no longer circulated to very high levels. Instead, viruses from the clade 2 continue to circulate and diversify. When we broke down these viruses into clade 2A and 2B, the 2022/2023 northern hemisphere season for the US was really predominant from this 2b clade. However, the majority of viruses since then have been from the 2A, one of its many subclades. 2A1 did have several detections between 2022 in the beginning of 2023, although this clade has also decreased

in circulation. And instead we see more of a bottleneck in that the vast majority of viruses circulating during 2023 have belonged to the 2A3A1 subclade. And this is a subclade represented by the A Massachusetts 18, 2022 and A Thailand 8, 2022 vaccine viruses. Our current vaccine virus for the Northern hemisphere is Darwin 6 2021 or Darwin 9 2021. And this represents from the 2A subclade. So looking at our phylo-geography about where the sub cades circulated and how those clades have changed over time. Restates what I said previously, that during February to August of 2023, we saw a lot of clade circulations from 2B, 2A1, 2A1B, 2A3, 2A3A, and 2A3A1 during this time period. And regional differences in which particular subclade of H3N2 predominated. However, you can see a trend that parts of East Africa, Middle East, South, and Southeast Asia and Oceania were predominated by the 2A3A1 virus. This continued this dominance and during the reporting period, September through January, you can really see that 2A3A1 circulated globally where we were seeing a little bit of differences in parts of West Africa, which still saw the circulation of a 2A3A. So very genetically related to 2A3A1, but not all of the same HA substitutions that I'll go over next.

In terms of the clade level, we saw a very specific 2A3A1 dominance during this reporting period. However, what we'd like to do is once we have one particular clade, we still like to split up the hemagglutinin by shared amino acid changes to look for whether or not there are changes in proportions within that clade and of course, looking at our different antigenic profiles to understand whether or not the new changes in the hemagglutinin can show antigenic drift. At this tree, we're looking at all of data collected since September of 2023. And again, at the base of the tree, what we're looking at are the 3As, and they share changes at position 96, which adds a putative glycosylation site, changes at 192 and 378. And at the very bottom here, you can see the 2A3 viruses that I mentioned circulated in parts of West Africa. 2A3A1 viruses share three additional changes that are of importance. This includes changes at 223, 50, and 140K. As you remember, the 140K on many of the subclades of 2A and 2B was a site that was undergoing convergent evolution. So we're seeing derivatives of the two A and clade two viruses

really accumulate change at this particular substitution. So if you look now at the phylogeography of where the different subgroups of 2A3A1 circulated we've broken them up into subclades J.1 to J.4

We'll start with the bottom of the tree for the J.3 and the J.4 subclades. These clades were much smaller in proportion and are have decreased in more recent months. But we're seeing in parts of Asia and Southeast Asia. And particularly the J.3 with the change position 501 with the predominant one of the predominant clades that circulated during China's H3N2 epidemic activity. You can see that the Thailand 8 and the Massachusetts are at the base of the 2A3A1s and don't have some of these additional changes that I'll mention. Now, if we look at more recent data, the J.1 and the J.2 subclades has had more detections. The J.1 share changes of 347 and 25. The J.2 share two main changes, and that includes a change of position 122, which potentially loses like a constellation site and changes of this position 276. Now, the vast majority of viruses that we're seeing in the more recent months belong to either the J.1 or the J.2. And you can see that by looking at where these particular subclades were circulating, we see a lot of J.1 in parts of Asia and Europe and a little bit in North America, but J.2, you can see parts of Oceania and West Asia, Central Asia, as well as Europe and North America in more recent months. So now that we're looking at the main changes between the subclades of J.1and J.2, but we're also starting to see in H3 and 2HA our additional changes in positions 45 and 124. Throughout the different clades. So as we continue to see H3N2 viruses, we're seeing continual genetic diversity within the human. Again, we're picking representative viruses across the genetic diversity for our further characterization. This shows a number of H3N2s antigenically characterized and as mentioned, we can see our collaborating center in Beijing did characterize quite a few due to their large H3N2 season, as well as our collaborating center in Melbourne that continue to see H3N2 activity during their reporting period. But all CCs have data for anogenically characterized H3N2s during this reporting period.

So this is our ferret antisera data in the HI assay, the hemagglutinin inhibition assay. Using the current prototypes for the Northern Hemisphere 2022/2023 vaccines. These are the 2A viruses represented by Darwin 6 for cell and Darwin 9 for egg. And now, depending on which collaborating center perform

the analysis, you can see different variations in the recognition of the H3N2s. Where some collaborating centers saw good recognition are particular in China, they saw pretty poor recognition to using ferret antisera to Darwin 6 against the H3N2s analyzed. So in all, we can see a reduction in reactivity for the total H3N2 viruses tested, either looking at the cell prototype or the egg prototype ferret antisera. Now, if we change the reference to be the vaccine prototype for the Southern Hemisphere to Massachusetts 18 2022, like for the cell or Thailand 8 egg excuse me for the egg that represents an HA from the 2A3A1 subclade. We see that all collaborating centers saw good recognition. Especially in China, you can see a much improved recognition of the H3N2s, which circulated during that time period. And overall a pretty good recognition of the genetic diversity of the viruses during this time period. And taking that ferret antisera looking at data from our collaborating center in Melbourne, again, using antigenic cartography, where one square shows a twofold production in in this case, either HI or FRA which is a type of neutralization based assay. We can ask the question. Now that we've broken up the different 2A3A1s into these subs antigenically, where does the Ferre erra put these viruses? Are they antigenically related? And we can see that the viruses that are in dark purple belong to J.1. Those that are J .2 are in pink, J.3 are in light purple, and J.4 are in a very light pink. And then viruses outside of the 2A3A1 are shown in brown or in a light tan. So in general, 2A3A1 viruses do cluster together. Although we are starting to see a little bit of separation between the J.1 and the J.2 viruses with our ferret antisera panels.

When we look at our neutralization based data, they're a little bit more tightly related in that assay. In this assay, we can show where the Thailand 8 cell and the Thailand 8 egg viruses are represented. And then in the next slide we can look at the sera circle for the Thailand virus showing for the most part good recognition across the 2A3A1 subs from J.1 to J.4. But we are seeing some viruses a little bit outside of that serum circle. So obviously these are ones that we're continuing to monitor and to see what particular substitutions they have and whether or not these genetic, variants continue to increase in circulation. But for the most part, the vast majority of 2A3A1 viruses fell within the serum circles for the Thailand 8 of 2022 like viruses. Again, the human sera data that we have is with vaccination for the

2022, ’23 season where the vaccine prototype was A Darwin 6 2021 like so the 2A virus. And as I mentioned the 2A3A1swere the viruses, which circulated predominantly globally but we also included viruses from the 2A1B and the 2B clades as well. Here's where we can see reductions significant reductions in GME titers. Among some viruses here, you can see across the 2A3A1s we have several groups, which showed reduction as well as some of the 2B viruses. This is again, adding information of how much breath would we get. If we maintained Darwin 6 like antigens in the vaccine, and since we're starting to see reductions in recognition, this again is part of the information suggesting that a vaccine antigen needed to be updated.

However, at this point, we don't have a post vaccination human sera with the 2A3A1like prototypes because vaccine campaigns for the southern hemisphere are just beginning. And so a summary of antiviral susceptibility, over 3000 viruses were analyzed and none showed genetic or phenotypic evidence of reduced inhibition. And we also have endonuclease inhibitor data. And of the over 1400 virus analyzed, there were four, which showed genetic or phenotypic evidence of reduced susceptibility to biloxivir. I also want to add that in addition to the data that I presented showing antigenic characterization against mainly the hemagglutinin. We also did analysis of the Nerminidase and showed that the Massachusetts 18 2022 and the A Thailand 8 2022 like Nerminidase actually well represented and recognized the majority of 2A3A1 Nerminidase genetic variation that we're seeing. So we had two bits of evidence that the vaccine antigen that was Massachusetts 18 would be well suited for 2A3A1 viruses.

In summary the data presented supported updating the 2024, 2025 Northern Hemisphere vaccine antigen to the Massachusetts 18 like from clade 2A3A1. Again, this is the same antigen recommended for the Southern Hemisphere coming up season. H3N2 viruses, circulated globally, however they predominated in Asia and Africa. And looking at our phylogenetic analysis the predominance of the 2A3A1 was really important. However, we're continuing to monitor the further diversification that's happening within viruses from this clade. Looking at our ferret antisera, we saw okay recognition in some collaborating centers with ferret antisera raised to Darwin 9 like 2A viruses. However, we did see

reductions against 2A3A1s in some collaborating centers. This recognition was improved when we looked at post infection ferret antisera raised against the 2A3A1 like vaccine prototypes. And looking at our human sera data, we've started to see reductions in significant reductions in viruses that are circulating from the predominant 2A3A1 plague when compared to titers against the cell vaccine prototype, Darwin 6, 2021.

Okay, moving on to influenza B viruses. This shows the detection of influenza B viruses since 2021. And again, as reported in last year, we hadn't seen a lot of influenza B activity. And you can see in lines yellow, the year of 2023 after February, there was significant influenza B activity in parts of Europe and Asia, and that activity continued during the Southern Hemisphere season. And as we looked to the Northern Hemisphere here, 2023, 2024 season, again, we saw significant co circulation and detection of influenza B viruses, and continuing to see high levels of detection in the current weeks. So a lot of influenza B activity being detected through GISRS. This graph shows the amount of data with the influenza B typing. Again, as mentioning, depending on the type of surveillance network, whether it's a clinical lab that doesn't perform influenza B lineage testing, and instead potentially has a full respiratory panel of other viruses as part of its testing algorithm, you're going to see a different level of viruses with lineage information. What we can see in 2020, this was the season where we had significant influence of B Victoria in the United States early in the season before the pandemic. What we're looking at is cocirculation of Yamagata and as mentioned before in 27 2018, there was more significant activity epidemics due to B Yamagata. But really in 2019, the amount of Yamagata was quite low and it's this light blue. It almost looks like this is the color of the X axis because you can see that since 2020, there has been no confirmed detections of Yamagata by GISRS. Instead, all of the influenza activity that's influenza B, and where lineage information is available, it's all B Victoria lineage reported. And again, including the large amount of B Victoria being detected during the 2023/2024 season.

This map shows again where there were areas of large epidemics due to influenza B. And while it's detected globally, we can see parts of the Caribbean and Central America and South America had

significant influence of B Victoria activity as well as parts of Africa and in more recent weeks, we can see China having a lot of activity to B Victoria as well as other parts of South and Southeast Asia.

In this pie chart, this accumulates the testing results submitted to GISRS and 0 B Yamagata viruses were reported during this time period. And 52 percent of the viruses that had a lineage test were B Victoria. So now I'll quickly go through the B Yamagata. As mentioned, there have been no confirmed detections of circulating B Yamagata 16 8 lineage viruses after March 2020. It remains the opinion of the WHO influenza vaccine composition advisory committee that the B Yamagata lineage antigen should be excluded from influenza vaccines as it's no longer warranted. However, as recommended in the previous vaccine recommendation where quadrivalent vaccines are still used, the lineage recommended for B Phuket, B Yamagata remains the antigen for the B Phuket 3073 2023 like virus.

Okay, moving on to B Victoria viruses. In the previous presentations we can see that the B Victoria virus hemagglutinin has undergone some major changes in the HA. This included both double and triple amino acid deletions in the hemagglutinin, which created very antigenically distinct viruses. We had cocirculation at one point of viruses from both the double deletion and the triple deletion clades. However, since 2022, the vast majority have been a subclade of the triple deletion viruses. In 2022/2023, we saw viruses from the 283A1 subclade, either from the 3A1 or the 3A2 viruses cocirculate. 2A3A1, excuse me, the 1A3A1 viruses were predominantly seen in China, whereas 3A2 viruses had global circulation. And we saw over time that continual detection and circulation of 3A2 viruses dominating throughout the southern hemisphere, throughout the northern hemisphere. End of season, the southern hemisphere 2023 season and the northern hemisphere 2023, 2024 season with detections throughout each geographic region. And this is exemplified again in this map showing where countries that have B Victoria viruses characterized during the different reporting periods. So a lot of countries providing both viruses and genetic information for B Victoria viruses during the two reporting periods, including the most recent September to January.

Now, looking at the hemagglutinin of the 2A3 viruses. They share three changes in addition to that triple deletion at position 127, 144, and 203. What we've seen is the predominance of an additional substitution at position 97. This has really increased in its predominance in the last reporting period. And so a good proportion of viruses now have this particular substitution. And we're starting to, again, see diversification in the hemagglutinin. And some regional differences in which additional substitution viruses circulated. So we're looking at convergent evolution at site position 183 and across a couple of different subline ages as well as changes of position 128 to different substitutions, and then a larger group with changes of position 129 as well. So again, we're taking representative viruses across the genetic diversity and looking further for antigenic characterization. And as mentioned, very few, 3A1 viruses were detected in China. This shows how many B Victoria viruses were antigenically characterized. And the, you can see that all WHO cloud ring centers energetically characterized be Victoria, but China our collaborating center in China, again, seeing a lot of activity in more recent weeks for B Victoria. Our ferret antisera to the B Victoria vaccine prototypes. That's the B Austria 1359417 2022 like for both the cell and the egg prototypes. In this case, we're seeing extremely good recognition across the WHO collaborating centers with ferret antisera raised to these viruses. So very little viruses with greater than eight-fold production in the HISA.

And looking at our antigenic maps, either from the collaborating center in Atlanta or in Beijing, the 3A2 viruses with or without that change at 197 are antigenically related and cluster tightly in the antigenic maps and cluster with the cell vaccine component for B Austria. What we can see at the bottom of the China the map from the China Collaborating Center are in darker green viruses from 3A1. And looking at the ferret, human, ferret serum circle to B Austria cell. We can see that the B Austria cell ferret antisera Assyria shows good recognition of all 3A2 viruses in both the Atlanta and the China Collaborating Center. And here's where you can see that reductions for the 3A1 being antigenically distinct from the 3A2s with ferret antisera.

Now moving on to post vaccination, human sera analysis again, multiple panels across different age groups. And what we're looking for are genetic diversity in the handbook then that shows changes in the geometric mean titer compared to the reference for the Austria. We saw good recognition across the genetic diversity across the genetic diversity of the 3A2 viruses tested with some of those additional changes in the hemagglutinin that I mentioned are circulating and cocirculating in different regions. For neuromidase inhibitors, over 1,600 were analyzed and four showed evidence of reduced or highly reduced inhibition. And when looking at endant and endonuclease inhibitors, none showed evidence of reduced susceptibility. Taken together, the data supported keeping the B Austria 1359417 2021 like antigen as the vaccine antigen for the 2024/2025 Northern Hemisphere season. B Victoria viruses cocirculated with Influenza A in all geographic regions. Looking at the genetics, 3A2 clade predominated, although there's been some additional accumulations in the hemagglutinin. But when looking at both ferret antisera and human sera. We're seeing good recognition of the genetic diversity in the hemagglutinin and of the 3A2 viruses.

With that, I'll end and again, thank all of the contributors from GISRS and CDC and other colleagues in getting data for this presentation. Thank you.

Dr. El Sahly: Thank you, Dr. Kondor for this very exhaustive overview and very clear presentation. I invite my colleagues to use the raise your hand function to ask questions to Dr. Kondor. And the first question comes from Dr Haley Gans.

Dr. Gans: Hi, thank you so much for that wonderful presentation. I guess I had a couple of questions. I know that the epidemiology slide was already presented in combination with what you're showing, which actually shows fairly good protection against the clades and types that we're seeing coupled with the low vaccine efficacy. I guess my questions are why do we see such low efficacy and were the cases done with those who had the vaccine versus those who don't and what is the escape really thought to be because the efficiency of the vaccine is not thought to be that high.

Dr. Kondor: I agree that with the VE studies, the test negative design, we are looking at the potential that an individual's either previous infection or vaccination history can influence how well they not only respond to the vaccine, but what are the estimates in that age population. So we're not seeing terrible VE, but it's still in the 40 to 60 range or a little bit higher for Influenza B of the when we look at our human sera data. For the US population where we have a human cohort, what we're looking at are actually doing a preselection and asking the question of individuals who had significant increase and four-fold increase in titer against at least three or four of the antigens in the vaccine. So we're asking good responders how well they're antibodies recognize the genetic diversity in the hemagglutinin. So we aren't able to know from our studies, the range in an actual responses to the vaccine in those studies. And so that's some of the data that, Dr. Grohskopf mentioned that we'll be looking into an RBE study is to understand some of the underlying population immunity that could be affecting RBE.

Dr. Gans: Great. Thank you.

Dr. El Sahly: Dr. Bernstein,

Dr. Bernstein: Thank you for that Dr. Wentworth like presentation. It was very clear. Thanks. I had two questions. One is, although it appears the decrease in Yamagata started before the pandemic. How did SARS CoV 2 disrupt influenza and contribute to the B. Yamagata becoming extinct?

Dr. Kondor: And so we don't actually have with 100 percent certainty the reason for B Yamagata no longer circulating. Some of my opinions are that, as we mentioned, the significant activity in 2016 to 2018 of B Yamagata really boosted population immunity to B Yamagata. Then at the same time, B Victoria was trying to stay relevant and so it was going through major antigenic drift changes by deleting different regions in the hemagglutinin, creating a very antigetically distinct set of viruses. That overtook B Yamagata in prevalence worldwide during 2018 to 2019. And so when we were going into the pandemic in 2020, we had very little B Yamagata in just a few countries with low level detections. So already to begin with, the amount of B Yamagata in the population was extremely low, and it was predominated by

B Victoria. So then we add layers of the mitigation strategies and lockdowns and really changes in behavior between all age groups during the pandemic, which really led to global decreases in influenza activity. And this, I think, is the added factor that we had the mitigation strategies for the COVID-19 pandemic, which really were effective in decreasing influenza circulation at the same time.

You're can hypothesize that you needed to still have initial seeding of the population to stay relevant. And in this case, this is overwhelmingly B Victoria. And again, it's an antigenic distinct B Victoria, but lower levels of population immunity, having a higher fitness advantage than the B Yamagata viruses that were previously circulating.

Dr. Bernstein: Thank you, and my second question then is how is reemergence or reintroduction potential of B Yamagata measured prospectively?

Dr. Kondor: So going forward, we're continuing to supply National Influenza Centers with assays to lineage type Influenza Bs and recommending that they continue to do B lineage assays. This is true, not only for the Global Influenza Surveillance and Response Network, but also for our US Virologic Surveillance. So, we're still going to be testing for it going forward. We're not going to all of a sudden stop our testing algorithms because I agree it's an important thing to continue to monitoring to have more certainty. But I hope I showed that all of the epidemics for Influenza B have really been only B Victoria since 2019. And so the real question is the risk that the committee was asking is what's the risk of a B Yamagata causing an epidemic? And at this point, we see that the risk is extremely low.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Portnoy.

Dr. Portnoy: Yeah. Thank you, Dr. Kondor. That was an amazing presentation. I have to admit, I'm always overwhelmed by all of the information. I understand maybe 60 percent of it and a lot of it I just have to take your word for the results. My question is, do we understand what factors lead to the development or emergence of these variations. Is it the virus attempting to escape already present

immunity? Are there environmental factors that make the virus may be more resilient to surviving? What is it that makes viruses develop variations? And have there been attempts made to use like machine learning to maybe predict future variations that might occur in the future rather than relying on epidemiology and retrospective information to predict the future? Can we predict the future based on what we've already know about the emergence of these variations?

Dr. Kondor: Thank you. Yes, so as previously presented at the different VRBPACs, the influenza viruses themselves actually are very error prone. What and they use that to their advantage. They're constantly making errors and in the errors, they're hoping that whatever actually still makes a replicating virus potentially confers some type of fitness against the other viruses that are circulating. So that continues to circulate. When we look at this, what we can see is that population immunity, again, it's either continuing to be both infection history as well as vaccination is really one of the major drivers of the selection process of which influenza viruses have a fitness advantage, but there's a whole bunch of other things in terms of what could improve the fitness of the influenza virus, including internal gene segment changes, reassortment, also the amount of activity of the different proteins as well. So we don't know all information, which leads to a fit virus. But again, it's that population immunity that's doing that major selection.

Now going to AI, I agree that we are at the beginning of understanding how to leverage artificial intelligence for not only a prediction of mutations, but potentially for fitness. And since I think what we have to understand is that big black box of other factors besides just mutations are really something that will be interesting to see how AI can adapt to understand since we still have a lot of factors that we don't really necessarily know influencing which viruses continue to circulate.

Dr. Portnoy: I look forward to those results. Sounds fascinating.

Dr. El Sahly: Dr. Janes.

Dr. Janes: Thank you also for really a very clear and really thoughtful presentation. I wanted to dig into the antiviral susceptibility. And can you help us understand the extent to which it's known whether or not, different subtypes are more associated with reduced susceptibility? And I guess I'm thinking, especially at the age three and two, which if I remember your slides showed a pretty modest meaningful rate of reduced susceptibility to some of the antivirals you tested. Am I remembering it was H3N2 with the higher rate?

Dr. Kondor: Yeah, so overall, the actual detection of viruses with reduced susceptibility to nervous inhibitors and to the polymerase inhibitors was extremely low. And so when we're looking at each individual subtype each year, we take representative viruses to understand the underlying susceptibility that viruses without mutations have and there are slight differences by subtype in the subtypes that we have in the IC50s, in those particular assays. But in general, there really isn't too much of a difference overall with what we're detecting for H1N1 and H3N2. Some of the major questions that we're actually answering with this is you can get resistance markers but within an individual. when they've actually been treated with an antiviral. But the real question is their community transmission of viruses with mutations, which confer resistance. And in this case, for all of the types and subtypes tested, we weren't seeing significant community transmission, which would have larger public health implications for mitigation strategies.

Dr. Janes: Thank you.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah, I had a relatively related question. First, thanks for a great presentation. It was very clear. During the pandemic, when there's so little flu circulating, were presumably all the changes that occurred in the virus was driven by what happens in birds. Was it was there, because there wasn't any changes in people because weren't any, there wasn't much spreading people. Do you have any sense for whether the rate of mutations changed at all? During the pandemic was in fact really all bird driven?

Dr. Kondor: So, for the human seasonal epidemics these were viruses which entered the human population from different sources in different time periods. So the H3N2s entered the human population in 1968 and the H1N1s which caused the 2009 pandemic have been circulating since 2009. And influence of these are really since we had known history for a detection of influenza viruses, potentially for a much longer. And so these genomes of the types and subtypes I just mentioned are strictly person to person transmission that are causing these epidemics. And the rate of change, the evolution is pretty consistent over time for influenza viruses. So what is circulating in birds are actually completely separate lineages and different range of subtypes. Although, I think you're well aware that there's been a large activity of H5N1 and H5NX globally, especially in the Americas in the last couple of years, which isn't a different phenomenon that we hadn't necessarily seen before the pandemic. And so that is something that our group that was studying the zoonotic influenza viruses have been very engrossed in looking at and seeing how those viruses have been circulating and changing over time.

Dr. Perlman: Okay, so then let me just clarify the question. So when there was so little human circulation of the viruses, was there less genetic change?

Dr. Kondor: So that was one of the interesting questions that we're still evaluating. When we looked at viruses that reemerged, when there actually was activity, as I mentioned with the H1N1s, it was a little bit interesting in that what we knew before 2020 was that there was a 5A2A1 virus with these typical changes. However, what continued to circulate post 2020 for these 5A2As that had significant changes in the hemagglutinin compared to its predecessor. So there was a lot of accumulation of changes. And so it wasn't as genetically related to its ancestor as we would necessarily expect, but not out of the realm of possibility for influenza with H3N2s. We saw multiple cocirculation before the pandemic and after the pandemic. So that really wasn't much of a difference than what we had seen previously. And with flu Bs as we mentioned with the B Victoria viruses, really that triple deletion virus of the 3As and the 3A2s, we have seen that before the pandemic as being a really fit virus and causing a lot of disease and that continue to circulate post pandemic

Dr. El Sahly: Dr. Pergam.

Dr. Pergam: Thanks again, Dr. Pergam. Great presentation really always. Learn a ton when we hear these. I had a question, and maybe this is a little bit out of the topic, but I wanted to follow up on Dr. Janes's comments related to use of antivirals, and I'm sure the WHO talks about this, but I'm curious about differential use within different parts of the world, since obviously there's some places that have less and more. Is there a particular focus within sort of data collection to look at high use areas in terms of resistance and development of resistance? And then a second question to that is where did we know where the resistance was detected? Was it worldwide or was it in particular regions? And the last is the question about biloxivir usage around the world because it seems like there's, again, some variance. And I'm not sure if this is data you have, but I'm just curious about use patterns and how that might affect some of the questions we have in this space.

Dr. Kondor: No, thank you. Yes. So we do have very limited data globally on which antivirals are actually in use. Specifically, even in the US, I'm not certain I can tell you how many doses of each of the different intervals have been prescribed or used. However, in some of our collaborating centers, specifically the WHO collaborating center in Tokyo, where there is more information on use of antivirals for both NIAs and biloxivir, we weren't seeing a higher rate of detection of resistant viruses. And in fact, looking at the global detection of markers with potential for changes in susceptibility, there wasn't a localization in a particular region. It was pretty much randomly detected. So that was not necessarily answering the question because we actually don't know how much of the antivirals are actually in use.

Dr. El Sahly: Okay. Thank you. I have a couple of questions. One of them, you alluded to in an answer to Dr. Perlman's inquiry, which is what's going on with the H7 and the H5s are we seeing spillover into humans and is there any signal that we need to worry about anything at this point?

Dr. Kondor: So there haven't been a lot of H seven activity in the recent year. But for H5, again, this is where we're seeing a lot of activity. And as I mentioned, it's H5N1, but there's also multiple NA subtypes

that are cocirculating and where we're seeing spillover are in areas where you still have much higher person to poultry or person to bird contact specifically in parts where you're still have live birds being bought and used for cooking. However, when we look at our surveillance data in the United States when we do have outbreaks of H5N1 on large poultry production farms, we are still continuing to do surveillance on individuals who are part of the mitigation strategy and culling operations. And here we're seeing it's not really spillover when proper PPE is used in these types of situations.

So what we do see is still significant detection of H5 globally and it's not just regionally, like it was in the previous decade. We're really seeing more global expansion into different types of birds, both wild and migratory birds, as well as poultry outbreaks, and then poultry to mammal spillover events as well. And so a lot of different surveillance networks are in place. As I mentioned, the WOA, the FAO, the OIE, OFLU, excuse me, and our USDA colleagues are part of a large global effort for influenza surveillance in animals.

Dr. El Sahly: Okay, but adaptation mutation that allow mammalian transmission, are we seeing an increase in those? This is a warning sign, but not for sure.

Dr. Kondor: Yeah, so there are specific markers we can look in some of the polymerase genes, which we have seen before be more adaptation to growing better in a mammalian. And we are seeing detection of these particular mutations, but I'm not sure exactly in terms of a magnitude of increase, whether that's been significant.

Dr. El Sahly: Okay. And if I go back to slide 32 there was a difference in terms of HAI versus news, in terms of where the circle is drawn, meaning when you look at the relatedness using the neutralizing antibodies. The Darwins and the new ones are much more related than when you look at them with the HAI, where the spread is much larger which probably is not the first year this has happened. Do we know the predictive value of one versus the other if we were to follow sequentially what happens during the season. In terms of VE, in terms of especially VE against the serious outcomes?

Dr. Kondor: We're not necessarily able to correlate the reduction seen in HI to VE or the reduction seen in our virus, neutralization assays to VE. But we are able to see, the two different types of assays that we can see. Whether or not the reagents that we have in this case, the post infection ferret antisera. Those antibodies have different properties in the assays. So with the neutralization, we're really seeing whether or not those antibodies are going to neutralize and prevent infection of the south. Whereas with the HISA, again, we're looking at the prevention of a sialic acid binding in the hemagglutinin. So slightly different types of questions, but still asking the reagents that we're looking at, where are they binding and how are they having an effect to recognize and neutralize the virus.

Dr. El Sahly: I understand they measure two different things, and maybe there is no clinical correlation. But what I'm asking is there a clinical correlation? Meaning, if the decision was made not to change the virus in the vaccine based on the newts, right? Because the viruses were closely related by newts. Would we see a different outcome? Maybe it's that's why I was thinking about it in terms of previous years, because I suspect that this has happened in other years as well.

Dr. Kondor: Right. So each subtype in each decision process, we have that large list of data that we look at and you're right in some decisions we weigh differently the results. And so you're correct. Like, when we see significant reductions with ferret antisera, that's saying that there's a major epitope change on the head of the hemagglutinin that can potentially have serious energetic drift. And then we do a double check. We know that humans have a much broader immunity and make antibodies to more regions of the hemagglutinin then just, the head region in some subtypes. And so we really want to ask more about the population immunity underlying that and whether vaccination is actually going to create more breadth of response. And I always look at it as an iterative process where we look at the genetics. We look at the antigetic data with the ferret antisera. And then the human sera really helps us understand the population, what immunogen will this vaccine be and what kind of breath can we get from it? And so each year and each time the main reason for the decision changes between what type of results we get.

Dr. El Sahly: Okay, thank you. I see no more raised hands next. Thank you so much Dr. Kondor for being patient and for presenting this data so clearly. We have a 10-minute break on the agenda, which I think we were a very inquisitive committee with a lot of questions. We ate up six minutes out of it. So maybe let's reconvene at 11:35. Is that good? Eastern time.

Dr. Sahly: Welcome back, everyone. Next on the agenda is Dr. Anthony Fries. Dr. Anthony Fries will go over the DoD influenza surveillance and mid-season vaccine effectiveness. Dr. Fries.

DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness: Anthony Fries, Ph.D.

Dr. Fries: Is my camera on? No. Okay, great. Good morning, everyone. My name is Anthony Fries and I'm here today representing the DoD's Defense Health Agency. I sit at the defense centers for public health in Dayton, which resides at Wright Patterson Air Force Base in Ohio. I'll be presenting the results from a number of DoD influenza public health efforts, incorporating data from multiple partners across the DoD. Next slide, please. First, I'll give a brief overview of surveillance efforts. I'll then present data on mid-year VE estimates from two distinct populations we have here in the DoD, one estimating VE against influenza illness in DoD health care system beneficiaries, and a second study examining VE in our service member populations. I'll then briefly go over phylogenetic diversity and antigenic characterization for the isolates we've observed in the DoD populations this flu season. Next slide. Influenza surveillance is a large part of several public health initiatives throughout the DoD. These programs extend to over 400 locations in over 30 countries. In addition to monitoring U.S. military personnel and their health care dependents, we also facilitate public health relationships with foreign entities and local nationals. This work is essential as we closely monitor our active-duty military personnel for respiratory diseases like influenza, and in turn, we utilize these health encounter records for the analyses I'll be presenting today. Next slide. Okay. I think it's good. Yeah, there we go. Thank you. Many aspects of the network are facilitated by DHA's Global Emerging Infectious Surveillance Branch. Efforts spread across all six geographic combatant commands, with multiple laboratories within these regions. And when organizing these activities, we take into account the capabilities of foreign national efforts as well as what WHO

activities are ongoing. Next slide. So, influenza RT PCR data are collected locally and submitted monthly through DHA channels. And on this slide, the number of specimens positive for each circulating subtype are graphed on the X axis and the percent positivity's overlaid. The data on top are from our partners in Ghana, while data on the bottom represent the flu net aggregated influenza activity in this region from WHO gist (phonetic) efforts. We show this slide only to illustrate that these DoD efforts can provide a significant contribution to regional testing efforts, and can be considerable sources of data for a region.

Next slide. Alternatively, data from these surveillance efforts can also provide key insights into where to direct characterization efforts when patterns deviate from global patterns, as shown here from our Asian colleagues. Next slide, please. So, the data. On this slide, we're showing CDC ILI cases as a percentage of total outpatient visits on the Y axis here on the left. You should be familiar with this one. on the right or the analogous DoD data, and this season within the U.S. we observed similar trends to the CCD. With a week 44 to 46 uptick in ILI, above our baseline, and continuing to hold above this baseline through at least week six so far. So pretty consistent with the ILI representation from the CDC flu view on the left. Next slide. So, armed with these background details, I'd like to transition to our first vaccine effectiveness study. We'll go into the mid-season VE estimates from DoD healthcare beneficiaries, excluding our active-duty component.

Next slide please. the dependent or beneficiary investigation utilizes the DoD's global respiratory pathogen surveillance program, which leverages an infrastructure of greater than about 100 sentinel surveillance sites, heavily concentrated in the United States and Germany. The program requests systematic sampling of six to 10 ILI encounters, weekly, from each installation for subsequent lab confirmation. This is a test negative case control design, that Dr. Grohskopf appreciatively gave you the background on. Cases included specimens testing positive for influenza by PCR and/or viral culture. These data were gathered between October first through February 17th this year. We did not consider other respiratory testing when defining these cases, such as SARS-CoV-2 positivity. The case definitions for ILI presentations here included a fever and cough, or fever and two additional symptoms listed in that

second bullet, or a physician-diagnosed ILI. And these details are gathered from questionnaires collected from our partners at each patient encounter. Additionally, vaccination registries and healthcare records are used to confirm vaccination status.

Next slide, please. Controls were matched based on collection month and resulted in a roughly one to four case-control ratio throughout each analysis. We conducted analyses estimating BE against overall influenza, independence, children, and adults. Additionally, we estimated VE against influenza A and B as well as subtype specific H1 and H3. Next slide please. Some things to note, 77 percent of cases and controls originated from encounters in the U.S., with the remainder from our colleagues that launched to a regional medical center in Germany. In all, we had 158 cases, 479 controls with vaccination rates of 53 percent and 60 percent in these dependent groups, respectively. To be considered vaccinated, an individual needed to present 14 days or more after receiving the 2324 Northern hemisphere vaccine. In the figures on the right, H1N1 represented 36 percent of our cases, 23 percent influenza B and 14 percent H3N2, with the remainder being influenza A unsubtyped. And, to preempt the question, there were no B Yamagatas detected, and we do make an effort to lineage type every one of the B's that come through the network, but only certain laboratories do this type of testing as Dr. Grohskopf earlier pointed out about the differences between clinical and public health lab capabilities.

Next slide, please. Some demographic notes. There was no difference in the number of cases between males and females in this population. Additionally, this population does, even in the dependence, skew toward younger age groups, with 62 percent of cases occurring in beneficiaries 17 years of age or younger. Next slide, please. I'll go over this next slide please. And for sake of the ease of digestion of these numbers, I'll actually move on to the forest plot on the next slide, please. Our mid-season VE estimates against medically-attended symptomatic influenza infections confirmed in the laboratory, showed moderate protection against all influenza A for dependents at 32%, but this was not significant. VE against subtype-specific influenza AH1 and AH3 was also moderately protected at 40 to 54 percent respectively, but both of those were not significant overlapping the zero line there. VE against influenza B

was our highest estimate observed in this study, and was 67 percent and was significant. And these are consistent with the higher estimates in the CDC data presented earlier. Our VE estimates against all influenza for adults was moderate at 52 percent, and for all dependents was 35 percent. Both of these were significant. And these were generally consistent with the VE estimates against all influenza in outpatients, that ranged from 33 to 49 percent, shown earlier. And, for VE against all influenza in children, we estimated 43%, but this was not significant. And just to emphasize, these are early season estimates.

Next slide please. I'll now transition to the VE estimates on our active-duty service member component. Next slide please. First, I'll present a case test negative control design for outpatients. This was done using the active component personnel from across all military services, and these include recruits here. And including those stationed in the continental United States as well as those stationed in foreign locations, from December first through February 23rd. Cases are the result of service member ambulatory or outpatient encounters. As in the dependent study, influenza cases were confirmed by PCR and/or culture. But in this study, rapid test positives are used for cases. Controls were those health care encounters testing negative for influenza, by either PCR or culture. Negative rapid tests were excluded from identifying controls, however. Models in this study were adjusted for sex, age, prior vaccination, and month of diagnosis.

Next slide please. In this population, only quadrivalent inactivated vaccines was used. It's also important to note that our service member component population is highly vaccinated, as influenza vaccination is compulsory for active-duty personnel. 92 percent of subjects here would have been vaccinated against influenza in the prior five years. So, to Dr. Perlman's earlier question, this population is well-adjusted to commonly circulating influenza diversity through the vaccine and encounters in infections. Regarding cases, we had a total of 3,545 cases overall, with 2,794 influenza cases and 751 influenza B cases. Many influenza A cases in this study did not have subtyping performed, and so limited the power of our subtype specific VE calculations. Next slide please. Here you can see our percentage

breakdown by age groups, for both cases and test negative controls. As with the dependent VE estimates, please note that our populations skew younger and may limit generalization to the broader public and different age groups.

Next slide please. Here are the VE estimates against both Influenza A and B, as well as subtypes AH1 and H3. The only statistically significant mid-season VE was against Influenza A, any subtype, with an adjusted VE of 26 percent shown here. The VE point estimates against influenza AH1 and H3 showed some effectiveness, but did not reach statistical significance, for either H1 at 23 percent or H3 at 28 percent, in these mid-season calculations. Lastly, this mid-season assessment did not find the vaccine to be effective against influenza B ambulatory infections in this population. Next slide. We did, however, conduct one further study using a cohort design, to estimate VE against hospitalizations in active-duty component service members. Next slide, please. In this cohort study design, we only looked at hospitalizations and active-duty, across all services, from September first through February 14th. To Dr. Offit's earlier point, these would generally not be high-risk populations. Just to add, outcomes were defined as any laboratory confirmed influenza case in which the medical record indicated hospitalization, or in which a hospitalization record had an ICD 10 code for influenza in the first or second diagnostic code.

Next slide, please. Similar to the previous studies, cases were considered vaccinated if outcomes occurred 14 days after vaccination. Incidence rates per 100,000 person years were calculated, and a Poisson regression model was used to calculate adjusted incidence rate ratios, with additional adjustments for sex, age, prior vaccination, really any vaccine within the last five years, and month of diagnosis. VE estimates against hospitalization, as defined here, were adjusted the same as in the outpatient VE for active-duty component. Next slide. In the first outcome, we observed 47 lab-confirmed influenza hospitalizations in these populations, along with 17 additional cases pulled from encounter records in the active-duty population for the second outcome there. Here, regardless of outcome, the incidence rates of influenza hospitalization, among unvaccinated service members, was about twice that the rate of

vaccinated members. And, correspondingly, VE estimates against both outcomes were 46 and 54 percent, respectively, in this active-duty cohort, and were significant. And suggestive of moderate protection against these more severe outcomes in this population. Next slide please. So, we'll now transition to our file of genetic analyses, that will build off of the tremendous work that was presented by Dr. Kondor. Next slide. So this figure illustrates the footprint, by HHS region, of where our influenza sequencing originated from this year, with 655 collected and sequenced between August 2023 and February 2024.

Overall, AH1N1 was well represented across the U.S., with AH3N2 really only predominating in region seven in the central U.S. for our populations. We observed more influenza B in the southern U.S. compared to the Northern regions. Internationally, we observed more AH3N2 in Asian and African surveillance efforts, as mentioned by Dr. Kondor earlier, while our European data looked more similar to our U.S. data with AH1N1 predominating. Next slide, please. To orient you to our trees, time is represented on the X axis. More recent data are further to the right of the tree, and we flesh out this tree with a few reference sequence data going back to 2021. Coloring is based on subclade designation, but note we're talking about the same clade diversity that Dr. Kondor referenced. X's within the trees represent reference vaccine strains that we've included. Of note, we'd like to thank the Nextstrain team for their molecular epi tool that we always use for tree construction and clade designations. For the HA gene segment of AH1, we continued to see a diversification of subclades within 5A2A. Within 5A2A, as mentioned, 5A2A1 represented 68.5 percent of our H1 cases. With further subclades, similar to that, J1, J2 that was referenced for H3, there are C1 designations of subclades here. So, our subclade C.1.1.1, dominating with 216 of the 226 5A2A1s. This subclade represented by the 216A substitution is one that the egg propagated Victoria 4897 falls into, and represents the current 23-24 vaccine and was also chosen for the 24-25 selection by the WHO technical committee. The X below that one, in the teal color, right there at the base of the 5A2A1, is the cell in recombinant based Wisconsin 67, for which we only really saw a handful of, at tree percent of isolates overall falling into that C11 subclade.

The remaining sequences fell more broadly into 5A2A subclade, with 86 falling into C1. Around 5.5 percent of our H1 sequences fell into a C.1.7, which is way down there at the base of the tree. And you can see the X there. But it's sort of indicative of those substitutions D94N and T216A, that predominated in Australia and Indonesia and New Zealand, and about six of our 18 were from this Indo-Pacific region. But there were quite a few that we detected from our U.S. surveillance efforts. And so, Dr. Kondor had referenced those earlier, and just sort of pointing out that diversity was still circulating. Overall, all of these data are consistent with the earlier CDC data, as well as the WHO strain selection report. Next slide, please. We'll skip over the NA gene segments on all of these trees. Next slide. If we take a different look at these data over time, based on proportional representation of the two major clades, we can see 5A2A predominating prior to the season, until 5A2A1 became more abundant and leveled off at approximately about 70 percent, through January. And really has regressed, actually, back to a nearly 50-50 split in our recent data, with about 5A2A and 5A2A1 cocirculating here. Next slide, please. Moving on to the H3 glycoprotein. We see a similar high degree of diversity in our data sets, as to those shown by CDC.

Several competing subclades circulating within the 3C2A1B.2A2 clades, with the vast majority, as mentioned earlier, being from the 2A3A1 clade, with about 98.5 percent of the 202 isolates sequenced being from this clade. And if we dig down a bit deeper into defining that diversity, 44.6 percent of these were in the J2 subclade of 2A3A1, which is lighter purple, there at the top of the tree. I don't have a cool laser pointer. This clade being the one with that N122D substitution, that has the putative glycosylation site loss, as well as that 276E substitution that Dr. Kondor referenced. The next largest subclade we observed was that J1 subclade, right below the J2, which was consistent with other surveillance efforts that showed detection globally, and in particular in East Asia and Africa in our sets. The X at the base of this 2A3A1 clade represents the egg propagated Thailand-8 and cell and recombinant Massachusetts-18 likes, that were newly chosen for the 2428 Northern hemisphere selection, right there at the base of that purple grouping and clade. The last X, further towards the bottom of the tree, represents last season's 23-

24 vaccine component, A-Darwin-6, and A-Darwin-9, from the 2A subclade, which we have not seen at all this entire season. Next slide. Skip over NA, please. Similar to H1N1, if we take a look at the H3N2 clade distributions over time, we can see that 2A3A1 dominated all season, with really only one-off detections of other diversity, even considering the global footprint for our testing. Last point would be to just say that our newest data continues to increase proportionally in its representation of the J1 and J2 subclades, within the currently dominating 2A3A1, for which the Northern hemisphere 24-25 recommendations does cover well.

Next slide, please. As we move to the H.A. segment of B, B Victoria. Well, I'll just start. We can start by stating that we, too, did not detect any B Yamagata lineage viruses in our networks for yet another year. We tried. Within Victoria, we only observed if we focus on this one, the V1A3A genetic diversity. And, specifically, the 3A2 subclade, with the substitution 203R that Dr. Kondor had referenced, predominating. We did not observe any 3A1 viruses all season long. Within the 3A2 viruses, all of these viruses except one fell into the C5 subclade on the tree there, the largest clade represented there. And was defined by the D197E substitution, with a good bit of diversification that was highlighted by Dr. Kondor as well, in this subclade, to include the C51, excuse me, and C56. The C56 being within that D129N branch. The X here, just below the C5 clade, is the B Austria 3A2 strain, that has been the B Victoria component of these vaccines since the 22-23 season, and was again recommended for the 24-25. Next slide please. And, next slide. So, to summarize our DoD genetic sequencing data, H1N1 diversity leans towards 5A2A1, with some indication of equal proportions with 5A2A in recent data. The subclade C.1.1.1 predominates within 5A2A1, but is well represented in the antigenic data I will show you in a moment. For H3N2 diversity, the 2A3A1 clade has predominated, with subclades J1 and J2 further battling it out, kind of, within that clade. For B. Victoria, we only observed subclades of VA1, 3A2, with C51 predominating. And overall, these genomic sequencing data align well with those presented by Dr. Kondor, and are in the national databases, and have been highlighted in the WHO recommendation. Next slide please. Lastly, we'll transition to a quick overview of our antigenic data. These data we'll be

discussing result from high content imaging-based neutralization testing, or hint assays, that were discussed a bit earlier, not reference the methodology, but it's neutralization testing. Our samples were passaged through MDCK cells. And in these data, we are showing the highest dilution of ferrite antisera, generated against various vaccine or candidate viruses, which showed 50 percent neutralization of each of our DoD isolates. And so these antisera are kindly provided actually by our colleagues at CDC. Thank you.

In this figure, you'll see annotated points indicative of ferrite antisera, raised against former vaccine or candidate virus vaccines. And the relative ability of those antisera to neutralize viruses that we isolated in our network. So here, if you'll recall, the first ferrite antisera slide from Dr. Kondor, I want to emphasize that we do not represent any 5A1 viruses here, isolates here, and therefore, if you're thinking about that large circle she showed, we're in the heart of it. And the largest cluster here, or circle there at the top, in red, captures that C1.1.1 diversity I was discussing earlier. So, these neutralization titers are represented there. And the next two circles, green in the middle and yellow on the right, suggest other distinct clusters within that larger cluster. The takeaway here is that, post infection ferrite antisera against A-Victoria 4897, the egg component of 24-25, did not have reduced neutralization titers to any of our DoD isolates. Ferrite antisera raised against a Wisconsin 67, the cell recombinant component, generally had some tighter reductions, including a few that reached eight-fold. There were only a handful, though. And, in particular, this cluster one, on the right, which contains C14 and C15 subclade viruses, but those were really detected infrequently in our data. And as a reminder, the GMTs from HI testing, using the human post-vaccination pools, shown by Dr. Kondor, were not significantly reduced to Wisconsin 67. And so those data included some of this diversity shown here, so these should not be interpreted as antigenically distinct here. But overall, given the antigenic and genetic diversity we observed in our network, our data support the 24-25 Northern hemisphere recommendations for the H1 component. Next slide, please. And, we can go over the, if anybody needs the raw data. Next slide. Transitioning to H3N2.

Again, you'll see here the annotated samples are representative of ferrite antisera neutralization titers, raised against recent vaccine in candidates. The large portion of gray and beige points in the middle of this map are representative of all of our DoD viruses from 23 and 24, respectively, that were tested. One main takeaway here is that we did not observe any significant clustering among the wide swath of H3N2 diversity we had in our data, including those newer subclades, J1 and J2, when challenged with post-infection ferrite antisera, generated with the 23-24 A Darwin six and nine like components. And as a reminder, Dr. Kondor did show a few larger reductions in their data, that fell outside their eightfold radius that they were showing. But I think, however, that the main larger takeaway to focus on here, would be that ferrite antisera generated against the newly chosen 24-25 recommendations. The Thailand-8 and Massachusetts-18 did a great job, with rarely an eight-fold reduction observed in neutralizing antibody titers, regardless of diversity that we were testing. And so that all said, we did not test human post-vaccination serum pools. So we can't comment on the reduced titers observed for the 2324 A Darwins, against recent explosion of 2A3A1 diversity. But, just wanted to say that both the six, nine Darwins and the Thailand-8, Massachusetts-18 covered this well. And then given this antigenic and genetic diversity, our data would tend to support the 24-25 updates and recommendations out of the WHO technical committee. Next slide, please. Next slide.

And this is the last slide. We only tested a handful of influenza B viruses, but can state that for the viruses we did test, we saw no reduction in neutralizing titers, with post infection ferrite antisera raised against both egg or cell P-Austria 1359417, which was the recommendation. And so our data tend to support then the Northern hemisphere 24-25 recommendation, and continues to do… This virus does an impressive job of neutralizing the B-Victoria V1A3A2, and all subclade diversity observed in our network, at least. Next slide, please. And next slide. So, this work is an aggregate result of so many fantastic colleagues and public health professionals across the DoD. I'm honored to have represented them here today. And thank you for your time. Next slide. Just so that everybody gets up there. It is a big effort. Thank you.

Dr. Sahly: Thank you, Dr. Fries. I invite my colleagues to use the raise your hand function. Should you have a question to Dr. Freeze? Okay, I don't see any. I have more of a technical question. Do individuals, who are part of the either active or beneficiary groups, do they always get their testing at designated clinics, or it could be anywhere and outside your network, or?

Dr. Fries: I don't want to misspeak, and potentially Colonel Badzik may be able to comment as well, but most of them all have access to military treatment facility clinics and resources, on a base, or through the tri-care network of health care provided to DoD and their dependents. We attempt to capture most of our testing through encounters that occur when they present to a military treatment facility. We oftentimes are blind to any that seek outside if they go to get their vaccination elsewhere. Especially the dependent population, can go out to a CVS, or something like that, to get a vaccination.

Dr. Sahly: A vaccination or also they have a lot of different things.

Dr. Fries: Sure. Yeah, and we try to conduct it in a very systematic way, so that we have random representation when we do collect those. For instance, those six to 10 ILI encounters that we try to capture it. The hundred plus MTFs that we do go after, to define some of these populations.

Dr. Sahly: Thank you, Dr. Fries. Dr. Gans has a question.

Dr. Gans: Hi. Thank you, Dr. Fries. I enjoyed seeing some real time data. So, that's always very powerful. I guess, just along some of the same questioning, I wondered what percent of your dependent population-- you talked about the military population, which we know has a requirement. How well vaccinated are the dependent populations among these? I imagine they might follow suit, but I don't know if they represent the rest of the population and their vaccine rates.

Dr. Fries: So, we tend to see them go higher. I believe that the most recent national data showed 40 percent for the U.S. public. Somewhere in that range. I don't want to misspeak. I can say that in our study set here, in that first beneficiary population, that 55 percent of those individuals were vaccinated. And so, we tend to see a slight uptick in our dependent population being vaccinated. Whereas the active-duty

component that we referenced have a general goal, of by mid-December, around 90 percent of that population is vaccinated. Services can also submit their own requirements and set of goals, but usually by mid-January, even they're approaching 100 percent, or as close as they can get without exemptions. I hope that helps.

Dr. Gans: Thank you.

Dr. Sahly: Alright, thank you Dr. Fries. I want to invite now Dr. Manju Joshi. Dr. Manju Joshi is the lead biologist at the division of biological standards and quality control at CBER FDA. Dr. Joshi.

Candidate Vaccine Strains & Potency Reagents: Manju Joshi, Ph.D.

Dr. Joshi: Thank you, Dr. Sahly. And hello, everyone. Today in my presentation, I'll be covering the WHO recommendations for 2024-25 Northern hemisphere influenza vaccines, which will include the WHO recommendation for trivalent vaccines as well as what they have proposed for if somebody is making quadrivalent vaccine for certain regions. In addition, another important part or major part of my talk will be giving you an update or situation of the availability of potency testing reagents, for each of the recommended strains, because this is a very critical part to ensure that the reagents are available and the vaccine testing can continue unhindered. And lastly, there'll be just a single slide for some general comments, which are mainly directed to what's not for the committee, but mainly the manufacturers who are listening into the meeting. And I think it's my good chance to convey some of the messages in this forum. As the season begins, everybody has things fresh in their mind.

Next slide, please. So, for influenza A, H1N1, PPDMO9 like component, WHO recommended virus for 24-25 Northern hemisphere season vaccines are same as for those for 23-24 Northern hemisphere season, as well as they were the same like 2024 Southern hemisphere season. For egg-based vaccines, WHO recommended an A-Victoria 4897 2022 (H1N1) PDM09 like virus. For cell culture or recombinant-based vaccine, the recommendation was A-Wisconsin 67 2022 (H1N1) PDMO9. In the interest of time, and not to just have a long list of things here, I have included a link to the WHO global

influenza program, where the candidate vaccine viruses, their availability, and their sources are listed. So you can always get this information.

Slide, please. As we proceed, I'll go by one for each recommendation, and the situation of the reagents we have for testing of the vaccines. As far as potency reagents for the (H1N1) PDMO9 component for 2024-25 vaccines are concerned, since this strain was recommended in last season, even in the Southern hemisphere season, the reagent situation is good. Reagents have been made available. I have listed all the reagents. These are currently available from different essential regulatory laboratories, and I will give a highlight about what are available from CBER. So, for A-Victoria 4897, for an IVR238 reassorted from egg platform, CBER reference antigen is available, as well as the antiserum (phonetic) lots are available for testing. For the same reassorted, other URLs had prepared the reagents, which is MHRA in UK, TGA in Australia, and NIID in Japan. And those reagents are also available. And I think there's no point me reading all the lot numbers, but these are the full information, if anybody wants to look at any of these reagents.

For the cell platform, A-Georgia 12 2022 is one of the H1N1 PDMO like virus. From this group, and CBER had prepared last season a reference antigen for it. And anti-serum is, of course, common to both the platforms. So they are available for vaccine testing. The recombinant manufacturers had chosen to use A-West Virginia 30 2022, which is from the same group virus. And CBER had prepared a reference antigen as well as antisera for use in combination with this. So currently, the situation is that these reagents are available from us, as indicated, for XL and recombinant platform, and some of the agri-agents are also available from other ERL's.

Next slide, please. Coming to Influenza A H3N2 type, WHO recommended virus for 24-25 Northern hemisphere season vaccines is different from the last Northern hemisphere season, but it is same as for 2024 Southern hemisphere season. WHO recommended that, for egg-based vaccines, an A-Thailand A-2022 H3N2-like virus be used, and for cell culture or recombinant based vaccines, an A-Massachusetts-18 2022 H3N2-like virus be used. Again, the candidate vaccine viruses are available, a lot

number of those are available. And the CVVs and their sources are again listed on the WHO site indicated here.

Next slide, please. Coming to the potency testing reagents for the upcoming season, since this strain change had happened in 2024, Southern hemisphere key efforts were made to make the reagents, and they were made available. So, CBER had prepared reference antigen for an A-California-122 2022 SAN-022 reassorted, which is from this group, recommended A-Thailand-like group. Antisera was also made available. Similarly for the cell platform. The CBER had prepared an A-Sydney-1304 2022 reagents, and was made available to the manufacturers. For the egg platforms and another reassorted IVR 237 was also used by some manufacturers, and those reagents were made available by TGA and MHRA. So, at this point, I would like to point out that this is a new strain change composition, and we are ready here in DBSQC and at CBER, and we will work with manufacturers and all our ERL partners to prepare and calibrate any additional reference antigen as needed. If manufacturers choose to start using new viruses, there will be some recommendation, people for the recombinant vaccine would need another antigen, but we will work with them and make sure that the reagents are available in a timely manner.

Next slide, please. Coming to influenza B, which is B-Victoria-287 lineage, WHO recommendations have not changed for the past two seasons. We have the same strain from 2023-24 Northern hemisphere season, as well as in 2024 Southern hemisphere season. WHO recommended, for an egg-based vaccine, a B-Austria-1359417 2021 B-Victoria lineage like virus be used, and same was for both cell- and recombinant-based vaccines. Again, you can look at the list of available candidate viruses and their sources at the WHO website, shown here on the slide. Next slide, please. Coming to the potency reagents for the B-Victoria component of the vaccine, since this has been in circulation, it has been used in vaccine for the last two seasons. A fairly good amount of reagents are available from different eras. As far as CBER is concerned, CBER had prepared a B-Michigan 2021 which is the B-Austria-like virus. So, for egg platforms, CBER have prepared the reagents and they are available for cell platform, CBER had prepared a B-Singapore WUH4618 2021 reference antigen, which is from the B-Austria-like group, and

similarly for recombinant platform, also a reference antigen was available. For the ease of a lot of other people who are observing this, I have indicated all the reagent lot numbers for both reference antigen and antiserum, and these are available from us. In addition, other URLs do have, for the egg platform reagents as well, but cell and recombinants are from us, available to you.

Next slide, please. So coming to the most talked about, is the influenza B., what we call the second B strain, for quadrivalent vaccines, which is from B/Yamagata/16/88 lineage. WHO recommendation said that, in the regions where quadrivalent vaccines are used, B-Yamagata lineage component remains unchanged from previous seasons. So it has been there for 23, 24, 20-- I don't know how many years have gone by. It has always been a component of the vaccine. So, B-Yamagata, B/Phuket/3073/2013, B-Yamagata lineage-like virus is recommended for egg, cell, and recombinant-based vaccines. And again, you can look at all the candidate vaccine viruses, and their availability, their sources, at the WHO website.

Next slide, please. So since B-Phuket or B-Yamagata component has remained unchanged for the last several years, the reagents have been in use for a long time. So, for the egg platform, CBER has prepared a B/Phuket/3073/2013 reference antigen and antisera, and those are available for us. Egg platform reagents are also available from MHRA, TGA, and NIAID as well. For the cell platform, the reference antigen was prepared against a B/Singapore/INFTT-160610/2016 virus. This was prepared by CBER and it's still available, reference antigen and antisera, both. Another antigen was made for this group, which was a B/Utah/09/2014, is a cell antigen, and it was made a while back and if anybody wanted to use it, it is still available. For the recombinant platform, CBER had prepared a reference antigen as well, and those lots are still available from us.

Next slide, please. So, I'll just wrap this up by saying that I've given you a list of all the reagents which are available for vaccine potency testing. DBSQC and CBER are ready to be preparing any reference antigens, if some of the manufacturer decide to start using a new virus, we'll work with them and ensure that the reagents are made available to them.

I'm not going to go into every bullet on this. These are mainly for vaccine manufacturers, about how they should be handling their request for reagents or sending samples to DBSQC for testing. One thing I definitely would point out is the bullet numbers three and four, that if you have any inquiries regarding CBER reference standards and reagents, or you want to request reagents, this can be done at the CBER shipping request, on the email shown here. And, for the manufacturers especially, I would say that, always send us feedback or comments on suitability or use of reagents provided. Or if you have any other questions, or any other aspect of our services which you would like to discuss with us, or need any help on that, you can always reach out to us, because we have established a mailbox which is CBERinfluenzafeedback@fda.hhs.gov.

And lastly, I would say, the availability of a vaccine to the public in a timely manner is indeed a collective big team effort by all of us. And again, we like to work cooperatively with all the vaccine manufacturers, and we want to make sure that they have what they need, the reagents in a timely manner, so that we work towards a single goal of making sure that a vaccine is available to the public in a timely manner. So we all work as a team together. So, we look forward to a good and a smooth new season ahead. Thank you.

Dr. Sahly: Thank you, Dr. Joshi. Any questions for Dr. Joshi? If you raise your hand. I'm seeing none. Thank you, Dr. Joshi.

Dr. Joshi: Thank you.

Dr. Sahly: I would like to invite Dr. David Greenberg. Dr. David Greenberg is the interim vaccines medical head of North America for Sanofi. Dr. Greenberg will give comments from manufacturer representatives.

Comments from Manufacturer Representative: David Greenberg, M.D.

Dr. Greenberg: Thank you. Can you hear me okay?

Dr. Sahly: Yes, we can.

Dr. Greenberg: Okay, great. And, if I could have the slides pulled up. Super. Well, thank you. I have to preface this by saying that the hotel I'm in is about to test their fire alarm. If that were to happen, hopefully it will be a short period and I'll be able to get right back to the presentation. So, I sincerely apologize for that. Well, thank you for the opportunity to present the industry perspective for the 2023-24 and 24-25 Northern hemisphere influenza seasons. This presentation was prepared in collaboration with, and reviewed by, the U.S. Influenza vaccine manufacturers, AstraZeneca, CSL Seqirus, GSK, and Sanofi. I'm David Greenberg, Acting Vaccines Medical Head for North America for Sanofi. Thank you. Next slide, please. Here's my disclosure statement. Next slide. I'll start the presentation with these key messages, follow up with the details underlying these points, and then I'll finish up with concluding remarks.

As a reminder, the vaccines distributed in the U.S. during the current Northern hemisphere 23-24 season have contained a strain change of the H1N1 PDM09-like virus, compared to the previous Northern hemisphere and Southern hemisphere seasons. It is notable that since the COVID-19 pandemic, U.S. influenza vaccine demand and coverage rates have declined in the U.S., despite vaccine supply surplus. I apologize. We can just wait. Okay, I'm terribly sorry. Hopefully, it won't recur, but I'll go on mute if it happens again. It's notable that since the COVID-19 pandemic, the U.S. influenza vaccine demand and coverage rates have actually declined in the U.S., despite a vaccine supply surplus. Therefore, we'd like to emphasize that special care be used in communicating the TIV transition to maintain influence of vaccine confidence and acceptance as we go through this transition. Since WHO and regulatory meetings that took place during the summer and fall of 2023, industry has aligned with multiple stakeholders globally, and work closely with CBER on regulatory submissions to enable transition from QIV to TIV. In addition, operational and commercial preparations for the transition are progressing. We heard you during the Southern hemisphere VRBPAC meeting in October 2023, and I'm pleased to report that industry has, or will have, the necessary CBER approvals that have been agreed, by timing, with each manufacturer, for distribution of TIV in the U.S. for the Northern hemisphere 24-25 season.

Finally, we want you to be aware of continuing concerns with the impact of the Nagoya Protocol on seasonal and pandemic influenza vaccine manufacturing. Next slide please. By way of review of this season, that is ending this spring, in February 2023 the WHO recommended updates to the quadrivalent formulation of influenza vaccines for the Northern hemisphere 23-24 season. On the left side of this slide, we show the WHO recommendations, resulting in a strain change to new H1N1 PDM09-like viruses, for both the egg and cell recombinant-based vaccines. The right side of the slide shows that during the March 7th, 2023 VRBPAC meeting, this committee confirmed inclusion of each of the four strains recommended by WHO. There were no unusual delays in obtaining candidate vaccine viruses or reagents for the last Northern hemisphere seasonal campaign. Next slide, please. The graph on this slide provides the estimated number of doses of influenza vaccines administered to adults 18 years of age and older in the U.S. up to January 13th of each season. The information shown on this graph is based on national pharmacy claims data from IQVIA, which includes both medical and retail claims. Although the number of doses administered gradually increased each season, from 2015 to the pandemic season of 2020-21, demand has declined each season since 2020-21, which may reflect influenza vaccine apathy, hesitancy, or confusion, or questions related to availability of recommendations for new seasonal vaccines such as COVID and RSV. This decline has been observed among all age and risk groups. In the current season, the demand is even lower than during the few years prior to the pandemic. Of note, this decline has occurred in the face of consistent influenza vaccine supply surplus in the U.S. We are concerned about the transition from QIV to TIV, which could potentially give rise to further vaccine hesitancy. We call on your support and that of the CDC in providing clear messaging to accompany this transition, the most significant change in seasonal influenza vaccination in many years.

Next slide, please. This graph is derived from the CDC flu vaccine site, and it shows influenza vaccine distribution in the U.S. for the past five seasons. The top blue line represents the 2020-21 pandemic season, with a record 197 million doses of influenza vaccine distributed that year, that season. The bottom-most line represents the current 23-2024 season. As of February 3rd of this year, 157 million

doses of that vaccine had been distributed in the U.S., representing a decline of about 37 million doses compared to the same period in 2020-2021. The U.S. vaccine dose distribution has declined in response to lower demand and therefore lower coverage rates. The data in this and the previous slide indicate that despite oversupply of the U.S. market, demand has consistently decreased over the past three years. Next slide please.

This slide provides an overview of the QIV to TIV transition timeline, and it illustrates the industry's commitment to meeting the request by CBER, VRBPAC, WHO, and other global key stakeholders to execute the transition in a timely fashion. In the interest of time, I won't go over all the details, but I'll highlight a few points. Since October 2023, industry has worked closely with CBER in making the transition work in the U.S. for the Northern hemisphere 24-25 season. However, WHO, EMA, MHRA in the UK, and most other regulatory agencies around the world are targeting the Northern hemisphere 25-26 season, or later, for the transition. Of note, EMA has communicated that the transition will take longer because the situation in Europe is more complex compared to the U.S. But they are prioritizing the transition of live attenuated influenza vaccine to a trivalent composition. Throughout this process, industry has been committed to maintaining supply and access to influenza vaccines, and the need to maintain public confidence during the transition. Moreover, industry has proposed the development of a framework to plan for future changes in influenza composition, beyond strain selection, and has agreed to work on a draft. Next slide please. We would like you to be aware of several additional challenges as we head into the 24-25 Northern hemisphere season. By way of background, in January 2023, WHO provided an indication of human antiserum for H1N1, which enabled manufacturers to prepare at risk for the potential strain change for the Northern hemisphere 23-24 season. This season, the comparable WHO report ahead of the Northern hemisphere 24-25 season did not contain human antiserum information. However, in the future, understanding these data would enable additional preparation time. Furthermore, planning for the Northern hemisphere 24-25 season has been especially challenging, due to the rapid shift to remove B-Yamagata from all influenza vaccines in the U.S. Next

slide, please. As noted previously, we listened to your recommendation to remove B-Yamagata from all influenza vaccines in the U.S. as soon as possible, and I'm pleased to report that all manufacturers are prepared to transition to TIV for the coming season in the U.S. Industry has or will have the necessary CBER approvals, with timing that's been agreed with each manufacturer, for distribution of TIV in the U.S. for the Northern hemisphere 24-25 season. Industry work in close collaboration with CBER to rapidly submit regulatory files and respond to FDA questions related to the transition from QIV to TIV. However, the majority of countries other than the U.S. will not transition to TIV for the Northern hemisphere 24-25 season. Therefore, QIB will be distributed to those markets, and industry will request CBER to release QIB for some of those countries. As noted earlier, industry is preparing a first draft of a formulation change framework, to include input from a broad selection of stakeholders and organizations based on the lessons learned from the B-Yamagata removal. A workshop is planned to take place with WHO collaborating centers, essential research laboratories and industry partners in July. Next slide please. We think it's important that you're aware of ongoing concerns of industry with the impact of the Nagoya Protocol on seasonal and pandemic influence of vaccine manufacturing. Although the U.S. is not a signatory to the Nagoya Protocol, companies based here are still impacted by it. The sharing of pathogens and their associated information should be fast, easy, legally certain, but in recent years, the Nagoya Protocol or other legislation has made this increasingly difficult to achieve. National influenza centers continue to supply flu viruses, however there is often a lack of legal clarity if the viruses can be used for vaccine manufacturing and research. Of note, since 2018, supply of about 40 influenza viruses to manufacturers have been impacted. In recent years, to avoid delays and complexity given the tight seasonal manufacturing schedules, industry has used viruses from countries with a track record of timely approvals for their use. This adds an extra step and level of complexity for manufacturers, due to having to check legislation status in each country supplying candidate vaccine viruses. The impact is not only on supply of seasonal influenza, but also potentially on supply of pre-pandemic avian viruses. Next slide please.

In conclusion, here are the key takeaways from today's industry presentation. The current Northern hemisphere 23-24 seasonal vaccines contained H1N1, PDM09-like viruses that had changed from the previous Northern hemisphere and Southern hemisphere seasons. Since the COVID-19 pandemic, U.S. influenza vaccine demand and coverage rates have declined, amid vaccine supply surplus. Therefore, special care is required in communicating the transition from QIV to TIV, to maintain vaccine confidence. Industries working with partners to address coverage and confidence issues in collaboration with CDC third party organizations and other key stakeholders. Industry is aligned with multiple stakeholders globally, and has worked closely with CBER to transition from QIV to TIV. Industry has or will have the necessary CBER approvals, with timing agreed with each manufacturer, for distribution of TIV in the U.S. for the Northern hemisphere 24-25 season. A framework for future influenza vaccine formulation changes, beyond strain selection, is being developed and will be discussed at the next WHO coordinated meeting in July. There are ongoing concerns with the impact of the Nagoya Protocol on seasonal and pandemic influenza vaccine manufacturing. The focus has been to use viruses from countries that can provide rapid approval. However, in some seasons, the options have been limited. And, next slide. That completes my presentation. I thank you kindly for your attention.

Dr. Sahly: Thank you, Dr. Greenberg. Dr. Sarah Meyer has a question.

Dr. Meyer: Thank you so much for your presentation. I think it was really helpful to hear about the commitment from all of the manufacturers that supply the U.S., to transition during this season. You alluded to some of the challenges that might cause for vaccine confidence, demand, et cetera. But I do think having the full-- U.S. supply a single composition will help, from a program perspective, a communications perspective, and being able to share those messages to help maintain our vaccine confidence. My question, though, is, you outlined a number of steps that will be required to fully transition in 2024 for the U.S. market, and we know that sometimes things don't always go according to plan. And so I'm just wondering, from the manufacturer's perspective, some of the backup planning that might be done. For example, how confident are we that we will have a full and uninterrupted supply on

time for TIV? And if, for some reason, things don't go according to plan, what are some of those backup plans? Would we be able to revert back to quadrivalent for the U.S., in time with sufficient supply, and some of those other considerations.

Dr. Greenberg: So, for the coming season, as I indicated, all the manufacturers have or will have their approvals for trivalent vaccine. To that extent, this coming season really won't be different from a supply situation. Each of the manufacturers are expected to provide supply as needed to meet demand. So, I don't believe any contingency is needed for this season. As I say, the manufacturers have or will have their TIV licenses. Manufacturers are moving forward with the annual strain change submissions to FDA, which come in shortly, probably this week, and the manufacturing is continuing. So, I don't think there's a need for a plan B for this season. It appears that everything is in place.

Dr. Meyer: Thanks. That's very helpful.

Dr. Sahly: Dr. Perlman.

Dr. Perlman: Yeah, I had another kind of planning question. With all the new discussion of different vaccine formulations, do you envision that manufacturers are going to diverge in the kinds of vaccines that they're going to develop? Whether it be mRNA vaccines or any others? And how is industry planning to think about that?

Dr. Greenberg: Well, certainly industry is looking at keeping in mind and working on future influenza vaccines. You mentioned mRNA. There are others. There are discussions about the formulations of future influenza vaccines, again, that go beyond just a strain selection. But quantities of antigens, having, as discussed, I think, at the last meeting, around having perhaps two H3 viruses, two H1 viruses, depending on the epidemiology and surveillance. So each of the manufacturers are considering these on their own. I think you've asked a good question in how does industry proceed. Obviously, those are going to be research in the labs, and clinical trials, which, you'll know of through public disclosure. And discussions that each of the manufacturers will have with the FDA. So I can't predict what direction all of that is

going to go, but each of the manufacturers will progress in their research programs, clinical development programs, and then you'll see that in future years.

Dr. Perlman: Thank you.

Dr. Sahly: Dr. Chatterjee.

Dr. Chatterjee: Thank you. David, in sort of follow up to that question, can you shed any light on what industry manufacturers might be thinking about or working on in terms of combination vaccines with flows? So with RSV, with SARS-CoV-2. Are there any efforts that are ongoing that you can share with the committee?

Dr. Greenberg: Well, yes, industry is looking indeed at combinations. And again, I point you to clinicaltrials.gov and other public sources. Yes, so there are studies that have been started with influenza and COVID. And that's certainly an interesting pathway that industry may take. And then we'll assess the safety and immunogenicity of those studies before any further steps are taken. But yes, that's ongoing.

Dr. Chatterjee: Thank you.

Dr. Sahly: Any additional questions to Dr. Greenberg? Okay, hearing none, we will break for lunch. We are anchored by the OPH start time and that is 1:30 p.m. Eastern time. So, let's break and reconvene at 1:30 p. m. Thank you.

Open Public Hearing

Dr. Sahly: Welcome, everyone, to the open public hearing session. The open public hearing announcement, I will be reading that now. Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written and oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. I turn the meeting now to Dr. Paydar. Dr. Paydar?

Dr. Paydar: Great. Thank you, Dr. El Sahly. Before I begin calling the registered open public hearing OPH speakers, I would like to thank all OPH participants, on behalf of the FDA and the committee, for their interest in participating in today's VRBPAC meeting and sharing their views and comments. FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing session, during which interested persons may present relevant information or views. I would also like to add the following guidance that the participants during the OPH session are not FDA employees or members of this advisory committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this open public hearing session reflect the viewpoints of the individual speakers or their organizations, and are not meant to indicate Agency agreement with the statements made. With that guidance, I would like to begin. Every speaker will have five minutes to make their remarks. Let's begin with our first OPH speaker, Mr. Don Ford.

Mr. Ford: Hello, I'm ready whenever the slides are up. Thank you. Okay. Hello. My name is Don Ford. I have no conflicts of interest. I've not received any payment to make my comment. Next slide. I think it's fair to look at what has been accomplished with the flu vaccine and see a major success in general. But just because we experience some success doesn't mean that we don't have improvements to be made or problems to address. On one end, we see data that shows the vaccine significantly reduces the burden on healthcare. But even then, it means 31 million people sick in a flu season, causing hardship to not only our economic standing, but also the actual real people who keep our economy moving. And we can look

at generalized charts of flu vaccine uptake and only see small decrease in the pandemic, but we also see a flu season that is starting earlier and potentially lasting longer. Next slide. When we look more closely, we see a significant decrease in uptake in some of our most vulnerable groups. Why is this happening? There are a few possible reasons. The public is unclear on the risk, low perceived effectiveness, vaccine hesitancy has grown as a trend in some, that is adjuvant-based safety concerns fueled by anti-vaccine rhetoric.

In addition to that, antigenic shift makes selecting a strain for six months later very challenging. But there also has been a loss of confidence to government agencies and public health in general. Next slide. And this could be the start of a concerning trend if the flu season continues getting worse. There is even concern of a long flu or sequelae brought on from a flu infection, which could impact the 31 million people who were estimated to have seen an infection this season. Next slide. When compared year to year, the real-world effectiveness has been inconsistent, and this has chipped away at the public's confidence. I have a lot of data on the screen, but the point is that the aim of VE is too low. We look at years that are thought of as bad, like the 2014-15 season with a 19% VE. But years like 17-18 had a VE of 29% and still similar outcomes. Aiming this low is simply costing lives. If our aim is 50%, but that allows our VE as low as 29%, which create results similar to 19%, then the whole system is outside of a safe margin. We're so far in the red that we've lost the margin of error completely, making choosing the variant a losing battle. We need to get that margin of error back so that folks can be protected, even when things don't go as we hope they might. Next slide. Influenza might be downplayed by society, but it is an unpredictable enemy because of antigenic shift. And the timing required for all the different vaccines means you have to predict it more than a half a year before they're going to be administered. And overall, we've pushed the limits of traditional technologies. Next slide. But there have been some potentially helpful developments. Recently, the Oxford malaria vaccine saw a major improvement in efficacy compared to other malaria vaccines, jumping from roughly 20 percent efficacy to 77%. The effect of this vaccine was also longer-lasting and maintainable. This was done by using a newer advanced adjuvant we've recently seen in

COVID vaccines. Matrix-M is an example of a long sought after saponin-based adjuvant that augments the immune system in ways that benefit our immune responses. Remember, this was not the conserved epitope platform for the COVID vaccine. This was just using the Oxford antigen as an entirely separate group designed it, meaning this adjuvant could be expanded to other platforms. The testing for the malaria vaccine has been running already a few years, and has been administered on an entirely pediatric population, demonstrating that Matrix-M is safe to use on children, which will also hopefully expedite the expansion of Novavax's COVID vaccine to the pediatric market.

Next slide. It's very likely that this shift in real-world effectiveness could extend to the flu shot, and considering the challenges with antigenic shift, there might be an additional solution. Multiple exposures to Matrix-M have demonstrated a shrinking of antigenic range that is, again, separate from their conserved epitope platform for antigen. This means that multiple exposures could give a larger margin for error, while at the same time overcoming immune imprinting, that could make some more vulnerable if they get vaccinated every year. I point out a concept called infection block theory, because as we reach the limitations of our current technology, we run into theories that are backed by relatively good data showing that vaccinating every year is potentially making some folks more vulnerable. But not vaccinating vulnerable folks is not an option either. Luckily, we've learned a lot about our immune system regarding imprinting because of the pandemic, and much of that can be extrapolated to influenza because of the similarities of how our immune system reacts to viruses that use spike protein. This offers the opportunity to fix the effectiveness issue, address antigenic shift, and give regulators back that margin of error that is actual real people being protected. This could rebuild the public confidence that is needed to increase uptake. Next slide. We have reached the limit of our traditional vaccine capability, while at the same time, the inconsistent and often low effectiveness is possibly damaging the public's confidence in vaccines in general, as well as trust in public health as a whole. And that is triggering a reduction in uptake, making the most vulnerable people even more vulnerable. At the same time, regulators are asked to play psychic and predict an impossible future with very real-world consequences. Please consider

supporting any process to explore technological advantages and adjuvants that might improve not only our influenza vaccines, but others that haven't seen improvements in many years. With the extra challenges coming because of the effects of the pandemic, whether social or immunological, the earlier they're addressed here by these committees, the faster we can get to solutions that will actually protect folks. Thank you for your time.

Dr. Paydar: Great, thank you so very much for your presentation. Our next OPH speaker is Paul Hennessy. Go ahead, Paul.

Mr. Hennessy: Hi, my name is Paul Hennessy, member of the public, no association or financial relationship. No conflict of interest. I'd like to echo the previous speaker's comments, and support all of those and suggest that we're back looking to incorporating matrix into flu vaccines, as well as other vaccines. But, the efficiency of the flu vaccine varies wildly, and it's unacceptable to have a flu vaccine with efficiency this low. Now, the recent malaria vaccine has incredible efficiency thanks to the Matrix-M. I'm curious if the same can be done with flu vaccines as well. At the very least, it's worth studying. COVID itself has damaged the immune systems of millions of Americans, so there has to be more updates to common vaccines like the flu, in order to boost protection. Matrix-M has the potential to improve the flu vaccine and other vaccines such as MMRs. Additionally, I'd appreciate it if, in the future, FDA messaging with all flu vaccine is combined with the encouragement to use a layered approach of vaccination, clean air, and respirators, to best reduce transmission. Relying too much on a vaccine-only approach creates a mistrust when it fails. And when the FDA is promoting the season's flu vaccine and other vaccines, consider including a message that stresses a layered approach for the best possible protection. Thank you.

Dr. Paydar: Great. Thank you so much for your presentation. Thanks for participating in today's advisory committee and for sharing your views and comments. This concludes the open public hearing session for today. I hand over the meeting to our chair, Dr. Sahly. Go ahead.

Dr. Sahly: Thank you, Dr. Paydar. So, now we will be discussing the voting questions. Dr. Paydar, or the audio-visual assistance, to display the voting questions.

Dr. Paydar: Yes. Next slide, where we have the voting questions. Yes, there we go.

Dr. Sahly: Okay, this begins the discussion session. I know there may have been some questions left over from the morning. So, please use the raise your hand function should you have discussion points, questions to Dr. Kondor, additional questions to the FDA, to Dr. Grohskopf, to the industry reps. Y'all are usually a talkative bunch. Where are the questions? Okay, I guess I can be-- oh, Dr. Portnoy has one.

Dr. Portnoy: Actually, hello, yeah, I don't actually have a question. I just want to comment that the presentations have been extremely complete. The epidemiology is very convincing, and I would have no reason not to affirm these recommendations. I think that they make sense based on the epidemiology. The only controversial thing was the BFUCAT (phonetic) vaccine for the quadrivalent, and I think we were reassured that there are efforts underway to modify that vaccine - either make it a trivalent or something else. So I'm pretty comfortable with all three of these, and I just don't have any specific questions.

Dr. Sahly: Okay, great. Dr. Chatterjee, I see your hand.

Dr. Chatterjee: Yeah, basically, Dr. Portnoy said what I was going to say, Hannah. Which is that, the data that have been presented today by the WHO, by the CDC folks, by the DoD, are very compelling, in terms of the selection of the virus strains that need to go into the vaccine this year, and I have nothing else to add. And I suspect that's why you're not hearing a lot of questions from anybody, because it's pretty obvious that these are probably the strains that need to be in the vaccine.

Dr. Sahly: I mean, I want to link back to our meeting, what was it, six months ago and then 12 months ago, when the issue of removing the Yamagata came about in full force. We are pleased, at least I am pleased, that the timeline was shortened from what was projected, and at least for the public in the United States and other countries that are open to it, the individuals will be vaccinated against relevant viruses. The issue of uptake is concerning. And, I mean, we can postulate about the etiology. However, Dr.

Greenberg brought up the removal of the Yamagata as a potential deterrent or another factor that might push the uptake even lower. Arguably, it may be the opposite effect depending on the clarifications that can be given to the providers and the public, which is, we don't want to vaccinate you for a virus that's no longer in circulation for three, four years now. So, it has time to play out, and it may play out positively, in that the public health officials and the regulators and their advisors are following closely the EPI (phonetic) and acting accordingly. So, we will see how that goes. Any other comments or questions? Okay, so Dr. Paydar, looks like the committee has no further questions. So we will move to the voting session. I turn it over to you.

Dr. Paydar: Great, thank you so much. Joseph, if you could have the next slide, please. Only our 12 regular members and one temporary voting member, a total of 13, will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the voting questions for the record, and afterwards all voting members and temporary voting member will cast their vote by selecting one of the 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 have cast your vote, you may change your vote within the one-minute time frame. However, once the call has closed, all votes will be considered final. Once all of the votes have been placed, we will broadcast the results and read the individual votes aloud for the public record. Does anyone have any questions related to the voting process before we begin? I think we have been through this drill before, so we're ready. Okay, Dr. El Sahly, if you would be kind enough to please read voting question number one for the record.

Voting Question One

Dr. Sahly: Voting question one. Does the committee recommend a trivalent 2024-2025 formulation for egg-based influenza virus vaccines in the U.S. that contains the following virus strains: an A-Victoria-4897 2022 H1N1 PDM09-like virus, an A-Thailand-8 2022 H3N2-like virus, and a B-Austria-1359417 2021 B-Victoria lineage-like virus.

Dr. Paydar: Alright, thank you. At this point, Joseph will move all non-voting members out of the main room. For those non-voting members, please do not log out of zoom. It will take us a few minutes. We'll be back with you shortly. Joseph, let me know when all voting members are present.

Vote Results

Dr. Paydar: Okay, Joseph, I don't see the votes. I see the names, but not the votes themselves, although they're unanimous, so… Great. Alright, thanks everyone for waiting. This was a bit of a wait. We'll have to do it two more times. There are 13 total voting members for today's meeting. The vote is unanimous, as you can see, a hundred percent have voted yes. 13 out of 13. Here are the voting responses of each of the voting members. I'll read them aloud for the public record. Let's see. Okay. Dr. Perlman, yes. Dr. Badzik, yes. Dr. Berger, yes. Dr. Gans, yes. Dr. Chatterjee, yes. Dr. Offit, yes. Dr. Portnoy, yes. Dr. Janes, yes. Dr. El Sahly, yes. Dr. Monto, yes. Dr. Bernstein, yes. Dr. Meyer, yes. Okay.

Dr. Pergam: Excuse me, I'm sorry. It's Steve Pergam. I don't see my name on there.

Dr. Paydar: Okay. I was actually about to say something about that as well. I wasn't sure who was missing. I'm glad you said something. So, for the record, I'll say Dr. Pergam also voted yes. Correct, Dr. Pergam?

Dr. Pergam: Correct.

Dr. Paydar: Okay. Great. Thank you so much. Alright, we're going to move to the second voting question. Dr. El Sahly, if you could please read the voting question number two, for the record. Joseph, if you could display voting question number two. Thanks.

Voting Question Two

Dr. Sahly: Voting question two. Does the committee recommend a trivalent 2024-2025 formulation for cell and recombinant-based influenza vaccines in the U.S., that contain the following virus strains: an A-Wisconsin-67 2022 H1N1 PDM09-like virus, an A-Massachusetts-18 2022 H3N2-like virus, and a B-Austria-1359417 2021 B-Victoria lineage-like virus.

Dr. Paydar: Okay. Great, thank you so much. Everybody, stay on hold. We will be back with you shortly. Joseph, please let me know when all voting members are present.

Vote Results

Dr. Paydar: Great, thanks. Here are the voting responses of each of the 13 voting members. As you can see, the vote is unanimous. We have 13 out of 13 who have voted yes. I'll go ahead and read the votes for the public record if I can see the votes. We're good, okay. Dr. Perlman, yes. Dr. Badzik, yes. Dr. Berger, yes. Dr. Gans, yes. Dr. Chatterjee, yes. Dr. Pergam, yes. Dr. Offit, yes. Dr. Portnoy, yes. Dr. Janes, yes. Dr. El Sahly, yes. Dr. Monto, yes. Dr. Bernstein, yes. Dr. Meyer, yes. Okay. This concludes the voting question two, and we're going to move to voting question number three. If you could display that for the chair, so she would be able to read it.

Voting Question Three

Dr. Sahly: Voting question three. For U.S.-licensed quadrivalent influenza vaccines intended for ex-U.S. distribution, does the committee recommend the inclusion of a B-Phuket-3073 2013 B-Yamagata lineage-like virus as the second influenza B strain in the vaccine?

Dr. Paydar: Great, thanks. Joseph, let me know when all the voting members are present. Thanks everyone, for your patience. This is the last question for the day.

Vote Results

Dr. Paydar: Great. The vote is not unanimous this time. We have 12 out of 13. 92% of the committee voted yes; one out of 13 people have voted no. 8%-- I'll go read the votes for the public record.

Dr. Perlman: I actually think I mis-voted. I voted no because I thought we were talking about the trivalent. So, I really would vote yes.

Dr. Paydar: Okay. Alright. So we're going to clear that afterwards on the paper. But for now, I'm allowed to go ahead and read yes for you, Dr. Perlman, correct?

Dr. Perlman: Yes.

Dr. Paydar: Great. Dr. Perlman, yes. Dr. Badzik, yes. So we have-- let's go back. We have a unanimous vote. 100% yes. 13 out of 13. For the public record I have to say that. Dr. Perlman, yes. Dr. Badzik, yes. Dr. Berger, yes. Dr. Gans, yes. Dr. Chatterjee, yes. Dr. Perlman, yes. Dr. Offit, yes. Dr. Portnoy, yes. Dr. Janes, yes. Dr. El Sahly, yes. Dr. Monto, yes. Dr. Bernstein, yes. Dr. Meyer, yes. Okay. Thanks to everybody for your votes. This concludes the voting portion for today's meeting. I'll hand over the meeting to Dr. El Sahly for asking the committee for their voting explanations. Thanks.

Dr. Sahly: Okay, thank you all for participating in the discussions and the voting. I'm going to be calling on the names one by one for the committee members, the voting committee members, to provide any final comments or explanations for their votes. So, beginning with Dr. Pergam. Please unmute and put your camera on.

Dr. Pergam: Hi, can you hear me okay?

Dr. Sahly: Yes.

Dr. Pergam: Okay. Yeah, I really don't have much to add to what some of my colleagues said. I think this was a pretty straightforward vote. The data is pretty clear. I think we've been interested in this change for a bit, and so it's exciting to see it happen.

Dr. Sahly: Very good. Dr. Bernstein.

Dr. Bernstein: I echo what was just said. The data seemed to support this decision. I was happy to hear that reemergence potential of B-Yamagata will be measured prospectively. And I think this is the right decision at this point.

Dr. Sahly: Great. Thank you. Dr. Monto.

Dr. Monto: I think we've come a long way in about 6 months since our last meeting, when we heard that it might be impossible to exclude the B-Yamagata from the vaccine, even though it had stopped

circulating, at least in the United States. And I think we should congratulate both FDA and the manufacturers of making this possible, because the problem seemed to be totally logistic. I think we need also to pay attention to what Dr. Greenberg said about misinterpreting our action. As, not getting rid of something that was causing a problem in the vaccine, but getting rid of something which was unnecessary. In the vaccine we're in a very difficult period now where there is increasing inappropriate suspicion about our vaccines. And I think we can make this as an example of how we can respond appropriately to changes in ecology and epidemiology. Thank you.

Dr. Sahly: Thank you. Dr. Janes.

Dr. Janes: Not much to add. This was a straightforward vote, as far as I could tell. I just want to echo Dr. Monto's comments, that I think huge congratulations goes to the FDA and the manufacturers for making this happen on a faster timeline than anticipated. And for the clear presentation in terms of the science as well. Thanks. Thanks to all the presenters.

Dr. Sahly: Thank you, Holly. Dr. Portnoy.

Dr. Portnoy: Not much to add. It's obvious that the data supported the vote, and I think the voting reflected that. I do look forward to the day when we can use artificial intelligence to predict emergence of variant strains and maybe proactively start developing vaccines for those strains before they even catch hold. I think someday that may be a possibility. Not yet, but I look forward to that. Thank you.

Dr. Sahly: Thanks. Dr. Offit.

Dr. Offit: Yeah, I agree with Dr Monto. I look forward to moving forward with vaccines for the rest of the world that don't contain a strain that appears to offer no benefit. Thank you.

Dr. Sahly: Thanks. Dr. Chatterjee.

Dr. Chatterjee: Yes, thank you. I don't have a lot to add either. But I do want to echo the concerns around the reduced uptake of influenza vaccines. I think this is something that is critically important. And the

messaging around the change in the vaccine formulation, I think, has to be done very carefully so that the public, or the providers of the people who are going to be counseling folks around vaccines, understand and are able to communicate the message effectively.

Dr. Sahly: Dr. Gans.

Dr. Gans: Thank you. I just had a couple of comments to add to that. I think there's been several positive effects that we actually saw from the work of this committee, and the FDA, and our partners. One of those positive effects we saw, obviously, with the Yamagata being removed and expedited. And I agree that really should be messaged as our ability to make changes according to the data that we see. And the other change that I thought was really positive, just from these discussions and having these sessions, is that more of the strains are actually being tested. So we've always had a concern about the unidentified, and what they actually represent, and are we missing something? And it's really nice to see how the availability of testing platforms have gotten out to our collaborators. And so we have more and more data to go on. I think what was really interesting about the Yamagata was that it was already decreasing before the pandemic, obviously, then we didn't see a resurgence, which I actually think is important data to consider. That it wasn't just a pandemic effect. And hopefully, obviously, not come back, but we have good testing platforms to discover that, if it does. I also think that it's important to put the vaccine efficacy in context. Once again, we know these aren't sterilizing. We know people can still get infected, and it continues to show good efficacy for severe disease and hospitalizations, which I think again is really our goal of vaccination, is to keep our populations as healthy as possible. And maybe with that messaging, we really can get some increased public interest in having these vaccines, because, as was mentioned at least from what we see in hospitalizations and children, you can't always predict. So you can't always just give it to high-risk individuals. And we had quite a bit of hospitalizations this year in our unvaccinated pediatric population. I think also, just lastly, what really encouraged me was hearing that the industry and other partners, because some of this is done through NIH-supported efforts, are really looking at new

platforms, as we've learned a lot lately and the science has advanced. And so, I would just really encourage the continuation of understanding how to formulate vaccines, to be more effective. That's all.

Dr. Sahly: Alright, great. Thank you. Dr. Berger.

Dr. Berger: Thanks. You know, at this point, after everyone else has spoken, I'm not sure I have anything to add of substance. I'll just reflect a little bit of what you've already heard before. You know, this was a pretty straightforward determination, at least on my end. The evidence really spoke to these being the strains we need to try and be protective (phonetic) against, in the new vaccine composition. And I'm very glad to see that we are no longer going to be including, at least in the U.S., the Yamagata strain, as we really should be focusing on including vaccine components that are actually going to be offering benefits to individuals. That's it.

Dr. Sahly: Dr. Badzik.

Dr. Badzik: Yes. So, hang on a second, I'm trying to get my camera turned on. No, I really appreciate the opportunity to be part of this forum and kind of echo what's been stated previously with regards to, you know, presentations were excellent. And I think the data was very compelling and you know, made the decisions fairly straightforward. But I'd also like to really echo Dr. Monto's comments with regards to moving to a trivalent. And I personally think that there's a lot of opportunity to leverage this, to rebuild trust within the community, especially those who are vaccine hesitant. Showing that vaccination isn't just to put more things in individuals' arms, but also just to address the current circulating strain. I think from our standpoint, as far as the Department of Defense, this has come a long way, of positioning us to actually improve our messaging and reach those that are expressing the vaccine hesitancy. Thanks.

Dr. Sahly: Thank you. Dr. Perlman.

Dr. Perlman: Yes. So, I think I'm last, or pretty close to it. So I do not have very much to add. I think everything's been said. I think the data were convincing. And I also agree, both in this situation and all the

vaccine issues that we deal with, that we have to be advocates for making it clear why we think vaccines are good and why they're important. And that's all I have to say.

Dr. Sahly: Thank you.

Dr Meyer: I might actually be the last person. And just echoing all the other comments, I think the data were very clear, presented in a compelling way. I think it shows our ability to adapt as the science adapts. I think this highlights the importance of the very strong surveillance that is being done to monitor strains. It was really reassuring to hear that this surveillance for Yamagata would continue, so that we could pick it up in the future. And I also thought it was really great to hear how much progress has been made in terms of operational readiness, to roll out the trivalent this coming fall. Thanks.

Dr. Sahly: Great, thank you all. I also voted along the same lines as everyone, precisely for the same reasons. One additional thought I have is sort of zeroing in on what is going on in terms of reduced uptake, and the etiology, this decline is taking place. We all know it's post-pandemic, but we don't know why it's happening. It's probably the interplay of other respiratory viruses, the messaging around vaccination, against those other viruses, and the flu is probably interplaying into all of this. So, understanding who's taking the vaccines, who is not, when it comes to serious infections, meaning infections landing individuals in the hospital or in the MICU. I still think that those data for flu and other viruses can benefit from a renewed approach with more vigor. Especially that, you know, sometimes you look at the same data, but two different countries make different recommendations. So understanding how it all is interplaying. Along with the other comments, my colleagues mentioned on the committee, would be great to learn about in the future. I want to thank you all for your patience and your votes and your comments. And I turn the meeting now to Dr. Kaslow (phonetic), who's going to provide the final remarks from the FDA.

Closing Remarks

Dr. Kaslow: Great. Thank you, Dr. Sahly. I'd like to start by thanking VRBPAC for the critical and probing questions on influenza vaccine composition, starting several convenings ago. VRBPAC's call to action to exclude the B-Yamagata lineage antigen component from the quadrivalent influenza vaccine, as soon as possible, was heard globally and by a broad range of stakeholders, culminating in the opportunity for today's vote to recommend trivalent formulations only for use in the U.S. It's a case study on the impact of VRBPAC and other advisory committees. It also well positions an orderly and timely switch to trivalent formulations, for all influenza vaccines, for use in the 2024-2025 respiratory virus season in the U.S. I'd like to thank the CBER advisory committee meeting staff and the technical staff that ran today, another flawless virtual VRBPAC meeting, fire alarm aside. Let me also thank all the invited presenters and the open public hearing speakers. A big thank you to the staff and CBER for their year-round efforts on keeping influenza vaccine formulations current. And finally, we greatly appreciate the time and diligence of VRBPAC members and our chair, Dr. El Sahly. Well done today, and back to you, Dr. El Sahly.

Adjournment

Dr. Sahly: Thank you, Dr. Kaslow, and thank you CBER. So, I turn the meeting over now to Dr. Paydar.

Dr. Paydar: Great, Dr. El Sahly. For closing comments, I wanted to thank the committee and CBER staff for working so hard to make this meeting a successful meeting. I now call the meeting officially adjourned at 2:32 p.m. Eastern Time. Have a wonderful rest of your day. Bye bye.