Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

180th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

March 7, 2023

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

Participants

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Voting Members	Adam C. Berger, Ph.D.	Director, Clinical and Healthcare Research Policy, NIH	Bethesda, MD
	Henry (Hank) Bernstein, D.O., MHCM, FAAP	Professor, Zucker School of Medicine	New Hyde Park, NY
	Archana Chatterjee, M.D., Ph.D	Dean, Chicago Medical School	North Chicago, IL
	Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
	Hayley Gans, M.D.	Professor, Stanford University Medical Center	Stanford, CA
	Holly Janes, Ph.D.	Professor, Fred Hutch Cancer Center	Seattle, WA
	Arnold Monto, M.D.	Professor, University of Michigan	Ann Arbor, MI
	Paul Offit, M.D.	Professor, Children's Hospital of Philadelphia	Philadelphia, PA
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Stanley Perlman, M.D., Ph.D.	Professor, University of Iowa	Iowa City, IA
Consumer Representative	Jay Portnoy, M.D.	Professor, Children's Mercy Hospital	Kansas City, MO
Temporary Voting Member	Colonel Douglas Badzik, M.D., M.P.H.	Director, Preventive Medicine, Office of the Secretary of Defense for Health Affairs	Falls Church, VA
Temporary Non-Voting Member	David Wentworth, Ph.D.	Director, WHO Collaborating Center for Epidemiology and Control of Influenza, CDC	Atlanta, GA
Guest Speakers	Anthony Fries, Ph.D	US Air Force School of Aerospace Medicine	Wright-Patterson AFB, OH
	Lisa Grohskopf, M.D., M.P.H.	Medical Officer, Epidemiology & Prevention Branch, Influenza Division, CDC	Atlanta, GA
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	Elisabeth Neumeier, D.V.M.	Director, Technical Life Cycle Management for Influenza, GlaxoSmithKline	Germany
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Public Commenters	Sarah Barry	SAFE Communities Coalition	

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Call to Order and Welcome

Mr. Eley: Good morning. Today's date is March 7th, 2023. My name is Joseph Eley, a member of your AV support team for today's proceedings, and I'd formally like to welcome you to the 180th meeting of the Vaccines and Related Biological Products Advisory Committee. At this time, I would like to hand the meeting over to our chair, Dr. Hana El Sahly. Dr. El Sahly.

Dr. El Sahly: Thank you, Mr. Eley. Welcome to the public, to the committee members and the participants to the 180th Vaccines and Related Biological Products Advisory Committee meeting. During this meeting, we will be discussing the flu vaccine strain selection for the Northern Hemisphere for the season 2023-2024.

I want to remind our committee members that, during the discussion time, to use the raise your hand function so I can see who is ready for comments and questions, and I will call upon you upon that. Please unmute yourself and turn on your camera. I would like to turn the meeting now over to Dr. Sussan Paydar, the Designated Federal Officer for the meeting for the conflicts of interest statement and introductory remarks.

Dr. Paydar: Thank you, Dr. El Sahly. Good morning, everyone. This is Dr. Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer for today's 180th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone for today's virtual meeting. Today, the committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the Influenza Virus Vaccines for the 2023-2024 influenza season. Today's meeting

and the topic we're announcing the Federal Register Notice that was published on February 9th, 2023.

At this time, I would like to acknowledge outstanding leadership of Dr. Peter Marks, Director, Center for Biologics Evaluation and Research, Dr. David Kaslow, Director, Office of Vaccines Research and Review, Dr. Jerry Weir, Director Division of Viral Products, OVRR, and Dr. Sudhakar Agnihothram, Acting Senior Advisor to the Office Director, Office of Vaccines Research and Review. I also would like to thank my Division Director, Dr. Prabhakara Atreya, and her excellent leadership, and my team, whose contributions have been critical for preparing today's meeting, Ms. Valerie Vashio, Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to Mr. Joseph Eley in facilitating the meeting. 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 BPAC meetings.

Please direct any press media questions for today's meeting for FDA's Office of the Media Affairs at FDAoma@FDA.hhs.gov. The transcriptionists for today's meeting are Catherine Diaz and Deborah Dellacroce from Translation Excellence.

We'll begin today's meeting by taking a formal roll call for the committee members and temporary non-voting members. When it is your turn, please turn on your video camera and mute 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 with the next person. Please see the member roster slides, in which will begin with the chair. Dr. Hana El Sahly. Dr. El Sahly, can we start please? Thank you.

Roll Call and Committee Introductions

Dr. El Sahly: Good morning. Hana El Sahly, Baylor College of Medicine. I'm an infectious diseases specialist, adult id, and my research focuses on clinical vaccine development.

Dr. Paydar: Great. Thank you Dr. El Sahly. Dr. Paula Annunziato, our industry representative.

Dr. Annunziato: Good morning. My name is Paula Annunziato. I head Vaccines Global Clinical Development at Merck. And as was just mentioned, I'm the non-voting industry representative for today's meeting.

Dr. Paydar: Great. Thank you, Dr. Annunziato. Next is Dr. Adam Berger.

Dr. Berger: Here we go. Hi. My name is Adam Berger. I'm the Director of the Division of Clinical and Healthcare Research Policy here at the National Institutes of Health mission Dentist Assist by Training with additional training in immunology. Thanks.

Dr. Paydar: Great, thank you. Next is Dr. Henry Bernstein.

Dr. Bernstein: Good morning, everyone. I'm Hank Bernstein. I'm a Professor of Pediatrics at the Zucker School of Medicine at Hofstra Northwell. I have expertise in pediatrics and vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Bernstein. Dr. Archana Chatterjee.

Dr. Chatterjee:Good morning. My name is Archana Chatterjee. I have the honor and privilege of serving as the Dean of Chicago Medical School and Vice President for Medical Affairs at Roseman Franklin University in North Chicago. I'm a pediatric infectious diseases specialist by background and training with the special interest in vaccines. Thank you.

Dr. Paydar: Great, thank you. Next is Captain Amanda Cohn.

Dr. Cohn: Good morning. I'm Amanda Cohn. I'm a pediatrician and medical epidemiologist at the Centers for Disease Control and Prevention with expertise in vaccine preventable diseases and vaccine policy.

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

Dr. Gans: Good morning. I'm Dr. Haley Gans, Pediatric Infectious Disease at Stanford, and the director of our pediatric infectious disease program for immunocompromised hosts. And my research is at the host pathogen interface using immunology. Thank you.

Dr. Paydar: Thank you, Dr. Dans. Next is Dr. Holly Janes.

Dr. Janes: Good morning. My name is Holly Janes. I'm biostatistician by training. I'm a faculty member at the Fred Hutch Cancer Center in Seattle. And my specialty is vaccine evaluation.

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

Dr. Monto: I'm Arnold Monto. I'm at the University of Michigan School of Public Health, where I work on vaccine preventable respiratory infections and other respiratory infections that are not yet vaccine preventable. My main interest is influenza.

Dr. Paydar: Thank you so much, Dr. Monto. Next is Dr. Paul Offit.

Dr. Offit: Yes. Good morning. My name's Paul Offit. I am a Professor of Pediatrics in the Division of Infectious Diseases at the Children's Hospital of Philadelphia and the Pearlman School of Medicine at the University of Pennsylvania. And my expertise is in the area of vaccines. Thank you.

Dr. Paydar: Great. Thanks so much. Dr. Steven Pergam. I'm not quite sure if he has joined the meeting yet. Okay. We'll come back to Dr. Pergam if he's not available. Well, we'll go with Dr. Stanley Perlman. Dr. Perlman.

Dr. Perlman: Good morning. I am Stanley Perlman. I'm a Professor of Microbiology and Immunology and of Pediatrics at the University of Iowa. My specialty is in pediatric infectious diseases and coronaviruses.

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

Dr. Portnoy: Good morning. I'm Dr. Jay Portnoy. I'm a Professor of Pediatrics at the University of Missouri Kansas City School of Medicine. I'm an allergist immunologist in the division of allergy, asthma, and pulmonology at Children's Mercy Hospital in Kansas City.

Dr. Paydar: Thank you, Dr. Portnoy. Next, we'll do roll call of our temporary voting member and temporary non-voting members. Colonel Douglas Badzik, our temporary voting member. Dr. Badzik. You're muted. Okay. I'm going to move to Dr. David Wentworth while you're trying to figure out the audio on your part with Derek and Joseph. Dr. David Wentworth, our temporary non-voting member.

Dr. Wentworth: Thank you. I am Dr. David Wentworth, and I am the Branch Chief of the Virology Surveillance and Diagnostics Branch in the Influenza Division at the CDC. And I'm also our WHO Collaborating Center Director there.

Dr. Paydar: Great. Thank you so much. I'm going to come back to Dr. Badzik one more time, see if his audio is working now.

Dr. Badzik: All right. My name is Doug Badzik and I represent the Department of Defense. I'm a preventative medicine physician, and I'm also the Director of Preventive Medicine for the Office of the Secretary of Defense for Health Affairs.

Dr. Paydar: Thank you. Fantastic. Thank you. I'm going to also call on Dr. Pergam and see if he's in the room. If not, I can move on to the FDA. I believe he's not here. Okay. All right. So we have total of 15 participants, 13 voting and two non-voting members.

Conflict of Interest Statement

I'll proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record. The Food and Drug Administration, FDA, is convening virtually today, March 7th, 2023, the 180th meeting of the Vaccines and Related 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 7th, 2023. The committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza of virus vaccines for the 2023-2024 influenza season. This topic is determined to be a Particular Matter Involving Specific Parties, PMISP.

With the exception of industry representative member, all standing or 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.

Related to the discussions at this meeting, all members, RGEs, 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 research and development agreements, teachings 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 special government employees 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 and 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 committee.

With this meeting, we have the following consultant serving as a temporary voting member, Colonel Douglas Badzik, DoD representative. We also have Dr. David Wentworth from the Centers for Disease Control and Prevention, CDC, serving as a temporary non-voting member and speaker for this meeting. As a speaker and temporary non-voting member, Dr. David Wentworth is not only allowed to respond to the clarifying questions from the committee members, but also authorized to participate in committee discussions in general. However, he's not authorized to participate in the Committee of Voting Process.

Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting. Industry representatives are not appointed as a 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 consumer representative for this committee. Consumer representatives are appointed to 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 guest and industry speakers for today's meeting are as follows, Dr. Lisa Grohskopf, Chief Medical Officer in the Epidemiology and Prevention Branch at the Centers for Disease Control and Prevention, CDC, 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. Elisabeth Neumeier, Director, Technical Lifecycle Management, Influenza, Global Vaccines Manufacturing Science and Technology, GSK, Germany.

The speakers have been screened for conflicts of interest and cleared to participate as a speaker for today's meeting, as guest speakers. Doctors 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. Dr. Elisabeth Neumeier is serving as a guest speaker from industry to provide flu vaccine manufacturer's perspective to the committee. Dr. Neumeier is allowed to respond to the clarifying questions from the committee members following her presentation. However, she's not authorized to participate in committee discussions or voting process.

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 Conflict of Interest Statement for the public record. I now hand over the meeting back to our chair, Dr. El Sahly. Dr. El Sahly.

Dr. El Sahly: Thank you, Dr. Paydar. The introduction to the meeting will be now given by Dr. Jerry Weir. Dr. Jerry Weir is the Director of the Division of Viral Products at the Office of Vaccine Research and Review at CBER, FDA. Dr. Weir.

Introduction — Dr. Weir

Dr. Weir: Good morning and thank you. Welcome to our annual Northern Hemisphere Influenza Vaccine Strain Composition Meeting. As everyone knows, we do this every year about this time. You can go to the next slide.

The purpose of today's VRBPAC committee discussion is to review 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. After that review, the committee will be asked to discuss and then make recommendations for the strains of influenza A, both H1N1 and H3N2, and the B viruses to be included in the 2024 influenza vaccines that are licensed for use in the United States. Next slide.

You will hear a lot of data presented today. You'll get presentations from the CDC, from the Department of Defense, an update from CBER about the availability of critical reagents and vaccine viruses, and a presentation from the manufacturers of their perspective. This is a lot of data condensed into a short period of time, but it covers a lot of different things, including the

epidemiology of circulating strains and surveillance data from the US and around the world. The data will include antigenic relationships among contemporary viruses in candidate vaccine strains. The type of data will include hemagglutination inhibition and microneutralization tests using post-infection ferret serum, also HI and microneutralization tests using panels of sera from humans who have received recent influenza vaccines. You'll also see data from antigenic cartography, phylogenetic analysis of H1 and NA genes, as well as vaccine effectiveness data. Next slide.

As I said, we do this every year about this time. This slide reminds you of what we did about this time last year. On February 25th, 2022, and shortly thereafter on March 3rd, 2022, the WHO and the VRBPAC made recommendations for the influenza season that we're currently in, 2022-23. At that time, both WHO and the VRBPAC made recommendations for the Influenza A H1N1 strain as shown on the slide, an A/Victoria/2570/2019 (H1N1)pdm09-like virus for egg-based vaccines, and an A/Wisconsin/588/2019 (H1N1)pdm09-like virus for cell- and recombinant-based vaccines.

The WHO and VRBPAC recommended for the Influenza A H3N2 component of the vaccines an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- and recombinant-based vaccines. The WHO and the VRBPAC recommended an Influenza B component for trivalent and quadrivalent vaccines. It was B/Austria/1359417/2021-like virus from the B/Victoria lineage, and also recommended, for quadrivalent vaccines containing the above three vaccines viruses, a B/Phuket/3073/2013-like virus from the Yamagata lineage. Next slide.

More recently, in fact, just a little over a week ago, the WHO made a recommendation for next year's vaccine strains. In other words, this is for the 2023-2024 season. The WHO made

this recommendation and recommended the following for the Influenza A component, the H1N1 component. The WHO recommended an A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2022 (H1N1)pdm09-like virus for cell- and recombinant-based vaccines.

This differs from the previous to current year's vaccine for the influenza H3N2 component. The WHO recommended A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- and recombinant-based vaccines. The WHO recommended an Influenza B from the B/Victoria lineage, the B/Austria/1359417/2021-like virus, that was in the previous year's vaccines and also recommended, for quadrivalent vaccines containing the above three viruses, a B/Phuket/3073/2013-like virus from the Yamagata lineage. Next slide.

So with that as a background, as I said, you'll hear a lot of data to support those recommendations. The committee will be discussing which influenza strain should be recommended for the antigenic composition of the 2023-2024 Influenza virus vaccine in the US. This is the purpose of today's meeting. While the WHO makes global recommendations, it’s critical that all national regulatory authorities make the recommendations for the vaccines in their own countries. And that's the role of th VRBPAC in this process and the FDA in this process. The next slide.

I'm not going to read all of this, but what we do, as we do this every year, we have options for the VRBPAC to consider. And what we do is we start with the recommendations that the WHO has made, and we consider those. And the committee has the option of making those recommendations or recommending alternative vaccine candidate compositions for the H1N1,

the H3N2, and the Influenza B components. I'm not reading this slide because it's basically captured in the next slide, which will be the voting questions. If you can go to the next slide.

So this is the way we do the voting. We try to somewhat simplify it, and we do the voting in four pieces. For each, basically one vote for each subtype. And so the committee would be asked to vote first on the H1N1 component, then the H3N2 component, then the Influenza B component for trivalent/quadrivalent, and then finally a fourth vote for the quadrivalent vaccines to contain the fourth strain. And so, again, we start with a recommendation with the WHO and then go from there.

And so for question number one, for the influenza A (H1N1) component of the 2023-2024 influenza virus vaccines in the US, does the committee recommend: an A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2019 (H1N1)pdm09-like virus for cell- or recombinant-based vaccines?

For the second voting question, for the influenza A (H3N2) component of the 2023-2024 influenza virus vaccine in the US, does the committee recommend: an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines) and an A/Darwin/6/2021 (H3N2)-like virus for cell- or recombinant-based vaccines?

For the third voting question, the committee will be asked, for the influenza B component of the 2023-2024 trivalent and quadrivalent influenza virus vaccines in the US, does the committee recommend inclusion of a B/Austria/1359417/2021-like virus from the B/Victoria lineage?

And the final voting question will be for quadrivalent 2023-2024 influenza vaccines in the US, does the committee recommend inclusion of a B/Phuket/3073/2013-like virus from the B/Yamagata lineage as the second influenza B strain in the vaccine?

So those will be the questions that we'll face later in the day. That's all for the introduction. I'm happy to take any questions if anyone has any. Back to you, Dr. El Sahly.

Q & A

Dr. El Sahly: Thank you, Dr. Weir. I invite the committee members to use the raise your hand function in the zoom at the ribbon below. And the first question comes from Dr. Bernstein.

Dr. Bernstein: Thanks, Dr. Weir, for that overview. I just had a question. It seems that the Yamagata lineage has not had a prominent role. Has there ever been a quadrivalent influenza vaccine? Is it even possible where there might be three A strains and one B strain rather than 2as and two Bs?

Dr. Weir: No. The reason is because quadrivalent vaccines, as they're licensed, are for an H1N1, an H3N2, a B/Victoria, and a B/Yamagata strain. That's the way the licenses are set up. When the quadrivalents were licensed, we had to have data showing that the inclusion of that fourth strain did not adversely affect the vaccine performance or the quality of the vaccine. Similarly, if there were a change to induce something else, like occasionally it gets thrown around, could it be two H1N1 components, or it could be two H3s? There would have to be, first of all, a recommendation for that. But second of all, each manufacturer would have to amend their license to make sure that that was permissible. In other words, they would have to have data to support that. So we can't just make such a recommendation. It would involve a license change for each of the manufac. Does that help?

Dr. Bernstein: Yes. Thanks for the explanation.

Dr. El Sahly: One question pertaining to the H1N1. You indicated that it changed, but it's still Victoria, right? Like that's what we used last year, or this year. It's just —

Dr. Weir: Yeah, but they're actually different strains.

Dr. El Sahly: Okay. They just didn't change the name of it, the number changed?

Dr. Weir: Yeah. Yeah. There are lots of A/Victorias. Last year's was a 2570/2019. This one's a 4897/2022. So yeah, it all depends on where the strain is isolated, is where the designation comes from.

Dr. El Sahly: Okay. So that clarifies it. The H1N1 is different, y'all. Okay. Other questions?

Dr. Weir: Yes. Both the egg-based and the cell-based recommendations from WHO are different from last year. That's true.

Dr. El Sahly: Additional questions to Dr. Weir? I see no raised hands. Thank you, Dr. Weir.

Dr. Weir: Thank you.

Dr. El Sahly: Next on our agenda is US surveillance, which will be presented by Dr. Lisa Grohskopf. Dr. Lisa Grohskopf is a Medical Officer, Epidemiology and Prevention Branch, Influenza Division at the CDC. Dr. Grohskopf.

US Surveillance — Dr. Grohskopf

Dr. Grohskopf: Good morning. Thanks for the invitation to be here today. This will be a brief summary of 2022-23 US influenza activity, and also, as is traditional at this meeting, a bit of the preliminary 2022-23 VE estimates from the CDC networks. Next slide.

So we'll start with the US Activity for this season. The reports of data from CDC influenza surveillance networks are available online through Flu-View, which is updated weekly. Most of the slides here are from the most recent report, which is for the week ending February 25th, 2023. Starting with virologic surveillance, results of influenza positive tests are reported weekly to CDC from a large network of clinical and public health laboratories in the US. The

data on the left are from clinical laboratories and show the percent of influenza specimens or tests that were positive by surveillance week for several recent flu seasons, with the current 2022-23 season, represented by the red line with the dots superimposed. For 2022-23, the percent of test positives peaked in late November, early December at about 26%, which is comparable with many of the previous seasons shown, but higher than 2021, in bright red, for which you can see the activity, sort of hugging the X-axis. And we had historically low activity that season, also higher than 2021-22, which is in light blue. Note also that the peak of the current season's activity curve has shifted to the left earlier in the seasons compared with what is typical from the other seasons shown. As of the most recent Flu-View report, the percent of specimens positive has declined from that peak and is about 1%.

On the right, the other component of the system, the Public Health Laboratories, tells us about the influenza viral types and subtypes that are in circulation. From October 2022 through the end of this past January 23, 99.5% of specimens were Influenza A viruses. Overall, 76% were H3N2, which are in red. There is, however, appreciable cocirculation, at 24%, of (H1N1)pdn09, which is in orange. Yellow represents the flu A viruses that are not subtyped. So note, there's very minimal green, which represents the Influenza B viruses, in this graph, just a narrow sliver at the 12 o'clock position. As of the end of January, only 0.5% were flu B, all of which were Victoria lineage. Taking it a month further out in time, as of the most recent Flu-View report, which is the week ending February 25th, the overall cumulative breakdown of the A versus B is similar, with 99.3% A and 0.7% B viruses. Next slide please.

So next, influenza-like illness, or ILI, surveillance. These data are from ILINet, which is a large network of providers reporting weekly the percent of outpatient visits that were for ILI. So importantly, these illnesses are not all influenza specifically, they're not lab confirmed. There

are other respiratory viruses causing similar symptoms in this mix. However, tracking ILI activities provides some sense of potential flu activity from season to season. Looking at the current season, which is the line with the triangles, ILI activity peaked in late November/early December and declined subsequently. Like the chart in the last slides showing the percent of specimens that were positive for flu, the ILI peak for the season has shifted to the left earlier in the season compared with recent seasons. For the last several weeks, ILI activity is hovering just above the national baseline of 2.5%. Next slide please.

So next, long-term care facility surveillance. Long-term care facilities, or LTCFs, from all 50 states and US territories report data on influenza virus infections among residents through the National Healthcare Safety Network, or NHSN, long-term care facility component. During week eight, which was the week ending the 25th of February, 67, or 0.5%, of a little over 14,000 reporting facilities reported at least one influenza positive test among their recipients. This decreased by a little over 5% compared with the previous week seven. Next slide.

Influenza-associated hospitalizations. These data are from FluSurv-NET. This is data that is associated with lab confirmed flu associated hospitalizations, and it shows cumulative hospitalizations per 100,000 by week. Cumulative hospitalizations for this season, which is the curve with the superimposed dots, which is again shifted to the left, they leveled off at about 59 per to 60 per 100,000 population in recent weeks. Note here that 2again, curve is shift to the left earlier than other seasons. Also, the cumulative hospitalization rate is higher than that observed in 2020-21 and 2021-22. Next slide please.

The last two surveillance slides are on mortality surveillance. So this, the first one, is from the National Center for Health Statistics. These data come from death certificates and do not represent lab confirmed illnesses. As of March 2nd, 2023, 9.2% of the deaths that occurred

during the week ending February 25th, 2023, or week eight, were due to pneumonia, influenza, and/or COVID-19, which we abbreviate as PIC. This percentage was relatively stable compared to the previous week seven and is above the epidemic threshold of 7.3% for this week. Among the 2,202 PIC deaths reported for this week, 916 had COVID-19 listed as an underlying or contributing cause of death on the death certificate, and 34 listed influenza. While the current PIC mortality is due primarily to COVID-19, the proportion due to influenza increased from October through mid-December, decreased for seven weeks, and has been stable for the past four weeks. Next slide.

Finally, pediatric deaths. These data reflect deaths associated with laboratory confirmed influenza among children, which has been reportable in United States since 2004. Thus far, as of the ending February 25th, 117 pediatric deaths have been reported this season. This is unfortunately more than the 2020-21 season, for which one was reported, as well as 2021-22, for which 45 were reported. Next slide.

So as an overview summary, as of the week ending February 25th, 2023, influenza activity rose early in the US, peaking nationally during late November/early December, with the percent of test positive peaking at about 26%. Currently it's about 1%. Influenza A(H3N2) viruses have predominated with cocirculation of Influenza A(H1N1)pdm09 viruses. The cumulative influenza-associated hospitalization rate has leveled in recent weeks to about 59 to 60 per 100,000. 117 Influenza-associated pediatric deaths have been reported thus far this season. Overall influenza activity is increased compared with the previous two seasons. And influenza US activity is currently low. Next slide, please.

Before moving on to preliminary VE estimates for this season, I just want to acknowledge my surveillance colleagues who collect, analyze, and report this data every week and who assisted in preparing these slides. Thank you. Next slide.

So, shifting gears to interim Influenza vaccine effectiveness estimates for the 2022-23 season. These are preliminary data and, as is the case normally, interim estimates can change over the course of time as more data are available. The data that I'm going to discuss are from three CDC networks, NVSN IVY, and VISION. These data were presented recently at the February 22nd ACIP meeting by Samantha Olson, Nathaniel Lewis, and Mark Tenforde, who lead this work with their teams. And I want to thank them a great deal for their and their collaborator's work and also for the slides which follow. Next slide.

So again, these are preliminary results, interim estimates. They come from three networks which evaluate vaccine effectiveness against laboratory-confirmed influenza-associated outpatient visits, emergency department visits, and/or hospitalizations in different age groups, which we'll go over as we discuss each network. Next slide, please.

Now these are three separate networks and there are some differences, slight, in the methodologies and also the age groups and the specific outcomes that each network evaluates. But there are some commonalities to the three, which we'll go over here. In each, enrollees have acute respiratory illness and are tested for influenza data. Data here presented reflect dates from enrollment from fall 2022 to early 2023. The design in each is a test-negative design, which involves comparing the vaccination odds among case patients who test positive they have influenza A, confirmed by molecular assay, versus control patients testing negative for influenza and SARS-CoV-2.

The estimates presented are all for Influenza A here. As we saw in the earlier slide in the surveillance section, there really has not been sufficient circulation of Influenza B. Vaccination status is defined as receipt of any 2022-23 seasonal flu vaccine according to medical records, immunization, registries, claims data, and/or self-report. Vaccine effectiveness, or VE, is calculated in each of these as one minus the adjusted odds ratio times 100%. Next slide.

So the first one we'll cover is the preliminary VE estimates against influenza-associated hospitalizations and emergency department visits among children aged 6 months through 17 years from the New Vaccine Surveillance Network, or NVSN. So again, these are hospitalizations and emergency department visits, and this is a pediatric population. Next slide.

In this network, estimated VE against laboratory confirmed Influenza A in hospital and emergency department settings among children ages 6 months through 17 years overall was 49%. The point estimate was slightly higher at 68% for inpatient stays than 42% for the emergency department visits. And it was slightly lower at 45% for the H3N2 viruses compared with 56% for the H1N1 viruses. Although you can see there's overlap in the confidence intervals. All of these estimates are statistically significant. Next slide.

So to briefly summarize for the preliminary VE estimates from NVSN, through January 25th, 2023, influenza vaccination significantly reduced. Laboratory confirmed medically attended influenza with a VE of 68% against pediatric hospitalizations and 42% against pediatric emergency department visits. Important protection was noted against both H3N2 and H1N1 associated illnesses. Next slide.

For a second network, preliminary VE estimates against influenza-associated hospitalization among patients aged 18 years and older. So in this case, we have adults, and our

outcome is flu associated hospitalization. This is from the Investigating Respiratory Viruses in the Acutely Ill, or IVY, network. Next slide.

In this network, estimated VE against laboratory confirmed Influenza A in inpatient settings among persons 18 years and older overall was 43%. The point estimate was a bit higher, at 51%, for the younger group here, the 18 through 64-year-olds than 35% for those 65 years and older. Although they're still appreciable VE for the latter, older age group. Among those with an immunocompromising condition, VE was similar to the overall population at 44%. All of these estimates are statistically significant. Next slide.

To summarize preliminary VE estimates from IVY, through January 31st, 2023, influenza vaccination significantly reduced laboratory confirmed medically attended influenza with an estimated VE of 43% against adult hospitalizations. Important protection was noted among adults aged 18 through 64 years and 65 years and older and among immunocompromised adults. Next slide.

The last set of results are preliminary VE estimates against influenza-associated hospitalizations and emergency department or urgent care visits among persons aged 18 years and older from the VISION Network. So again, we have adults, and our outcomes are hospitalizations and emergency department or urgent care. Next slide.

There are two graphs for this network. We'll go with this first one, which is the emergency department and urgent care visits. We'll do this first. Overall, within VISION, estimated VE against lab confirmed Influenza A in these settings among adults aged 18 years and older was 44%. Point estimate was slightly higher at 46% for those 18 through 64 years than 39% for those 65 years and older. These estimates were statistically significant. Among the subset with an immunocompromising condition, estimated VE was 30%. You can see, if you

look at the columns with the numeric data in it, our numbers are smaller here, and the estimated VE is less precise, with the lower bound of the confidence interval at minus 2%. Next slide.

Within the same network, estimated VE against lab confirmed Influenza A in inpatient settings was 39% among all persons 18 years and older, and was slightly lower at 20% among the 18 through 64 years old group, relative to 42% among those 65 years and older. Among the immunocompromised subset, the estimated VE was 31%. All of these results are statistically significant. Next slide please.

To summarize the preliminary VE estimates from VISION through January 2023, influenza vaccination significantly reduced lab confirmed medically attended influenza with a vaccine effectiveness estimate of 39% against adult hospitalizations and 44% against adult emergency department or urgent care visits. Notable VE was observed across age groups and among immunocompromised persons. Estimates were higher this year than VE estimates against hospitalization and emergency department or urgent care visits from last season, 2021-22, which were each about 25% at the same VISION sites. Limitations here and also with the previous data discussed for IVY, we do not at this point have data by Influenza A subtype. Next slide.

So to summarize data overall from the three flu VE networks that were discussed here. Across three CDC flu VE platforms, we observed consistent influenza vaccine effectiveness for the 2022-23 season. Influenza vaccination provided substantial protection against inpatient, emergency department, and outpatient illness among all ages, and provided substantial protection among important high-risk groups, that is, those ages, 65 years and older and immunocompromised persons. Next slide.

So, in closing, I would just like to very deeply thank the colleagues and their collaborators who actually do this work from NVSN. And next slide. And from the IVY

network. Next slide. And from VISION. Thanks very much. That's the end of my presentation. I'd be happy to take any questions or afterward after the next presentation, as the committee wishes. Thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Grohskopf. I would like to invite my committee members to start using the raise your hand function to ask questions for the CDC. And Dr. Portnoy. First question from Dr. Portnoy.

Dr. Portnoy: Great, thank you. And thank you for that detailed presentation. It's very informative. One thing that constantly bothers me, we just got through reviewing RSV vaccines where the effectiveness was 80%. I've seen Covid vaccines where it's 90%, and yet influenza vaccines are consistently in the 30, 40, 50% range. Why are these vaccines so much less effective? Is it that the strains aren't being matched properly? Are the vaccines not inducing an adequate immune response? Or do you have any idea of why these vaccines are just so much less effective than what we're used to seeing with other agents?

Dr. Grohskopf: I think that possibly a better answer might be possibly provided by Dr. Wentworth. But one thing to note about it is that, in general with flu, particularly with flu A, in seasons when we have a good match, we tend to see VE in the 40-60% range. And it is true that that is not in line with a lot of the VE that we see for other pathogens, tetanus, HPV, many other things. However, we do have also a pathogen that's constantly changing. So even when on the whole thing seem like a good match, we don't have control over what the virus is doing on a continual basis. The strains are selected. Importantly, they have to be far early in advance so that the vaccine can be prepared on time.

Another important thing to note is that we do at CDC annually estimate the estimated burden averted by vaccination. And even in a season, one recent example is a 2017-18 season, which was fairly severe, and for which overall vaccine effectiveness was about 39%, does prevent substantial morbidity and mortality in terms of illnesses, hospitalizations, medical visits, and deaths. I'm less able to answer the question of why it is the way it is, other than the fact that we do have strain changes, or strain evolution, constantly over the course of the year.

Dr. Portnoy: Just imagine how many hospitalizations and deaths it could avoid if it was 80 to 90% effective. Just imagine. Thank you.

Dr. Grohskopf: Would be amazing.

Dr. El Sahly: The second question comes from Dr. Gans.

Dr. Gans: Thank you very much. I had a question about sort of the nuance of the more severe outcomes. You didn't talk about hospitalizations to the ICU, for instance, or mortality, in terms of vaccine effectiveness. I wondered if we had that more nuanced data in terms of some of the outcomes, particularly in pediatric.

Dr. Grohskopf: No, at least not currently. The network data that we have now are what are available. I will check on whether the networks that follow hospitalizations are able to sort out hospitalizations by relative severity, I guess, the main indexes as you would, as you suggested, for example, ICU versus not. So I will check on that and I can probably get an answer back to the committee today, if that's all right. But currently what we have is what we have. It is possible that some more data might be available, for example, about H3N1 versus, or sorry, H3N2 versus H1N1 later in the season. They're difficult to know. But these data are refined over the course of the year leading into the fall. So things might look a little bit different by them.

Dr. El Sahly: Hmm. Okay. Thank you. I have a methodological question, and it pertains to the first, well, the introductory slide. You indicated that the flu VE was calculated by excluding individuals who also had positive SARS-CoV-2.

Dr. Grohskopf: Yes.

Dr. El Sahly: And then my, my question pertains to the prevalent SARS-CoV-2 upon hospital admission and visits for all sorts of reasons during the November-December timeframe and up until now. We are seeing a lot of prevalence, SARS-CoV-2. And so these are people being admitted to the hospitals for any reasons, yet they're SARS-CoV-2 positive. I wonder if as a sensitivity analysis, or how would this data change if we analyze by factoring an estimate for the prevalence SARS-CoV-2. And did it exclude a lot of patients that way?

Dr. Grohskopf: That is something I'll have to check with the investigators on their network, that network about. The reason for excluding those patients is that, when this was assessed last year, the assessment was that including those who were positive for SAR SARS-CoV-2 introduce some bias into the VE calculation. So the cleanest way with which to deal with that was to, and it did make a substantial difference last season, for 2021-22. But I, and they have, they do. The group does typically do sensitivity analysis of with and without, but I would need to, just to be certain of what they did this year, I would need to ask them. So I will do that.

Dr. El Sahly: Okay. Thank you.

Dr. Grohskopf: By prevalence?

Dr. El Sahly: Yeah, by prevalence.

Dr. Grohskopf: Okay. Let me check on that. Sorry, Dr. El Sahly. Thank you.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yes. I had a similar question to Dr. El Sahly's question. So I was going to add RSV into the mix too, to see how dual infections was considered. And also the second part again with acquisition. So you showed data on adults with SARS-CoV-2 infection versus flu. Do you have similar data for pediatrics, and also throwing in RSV?

Dr. Grohskopf: Not that… RSV was not considered for this season yet. That I know. I don't know what is planned as far as the additional analyses for considering relative prevalence of RSV, but I can also check on that as well.

Dr. Perlman: And then also SARS-CoV-2 and pediatrics, do you have that information compared to flu?

Dr. Grohskopf: I don't have the information on the prevalence. No, I'm sorry.

Dr. Perlman: Okay. Thank you.

Dr. El Sahly: Thank you. Dr. Chatterjee.

Dr. Chatterjee:Thanks, Hana. Thank you very much, Dr. Grohskopf, for your presentation. I have two questions, and they're getting into the weeds a little bit. And the data sets that you presented from may not be able to answer the questions, but I was just curious if there are maybe other sources of data for these questions. The first is whether we have vaccine efficacy laid out by the type of vaccine that was used. So high dose adjuvanted versus regular dose vaccines. And the second question is around egg-based versus cell-based vaccines, whether there's any difference noted in the VE based on those.

Dr. Grohskopf: At present, we don't. Confirmation of vaccines received is something that occurs through the spring into the summer. There are times when there is enough information at the very end of the season, when the final estimates are being prepared for publication, when there are enough data. But as of right now, no. One limitation of this is that in general, the sites

have participated in these networks aren't dictated which vaccines to use. So we tend to not sometimes have very as high uptake of some vaccines compared with others. There is actually one extra slide I have that shows.

If it is possible to bring up the slide deck and if you'd like to see that, that shows what the relative utility of the use at least in one of the networks was. But essentially, what I can say is we don't have information yet, for example, on high dose versus adjuvanted. We have not had, in general, appreciable uptake of LAI VE in recent seasons to be able to do LAI VE independent estimates. There's been overall less use, for example, of recombinant than of the other vaccines so far. So at this point we definitely don't have that data. It's possible that some might come later when we have a better sense of vaccine use, but it's hard to predict how that will go at this juncture.

Dr. Chatterjee:Thank you.

Dr. Grohskopf: Certainly.

Dr. El Sahly: Thank you. I do not see any raised hands. Any final questions to Dr. Grohskopf? Okay. Hearing none. Thank you, Dr. Grohskopf.

Dr. Grohskopf: Thank you.

Dr. El Sahly: As always, very highly anticipated data with every season. Next on the agenda will be the Global Influenza Virus Surveillance and Characterization. Dr. David Wentworth, Director of the WHO Collaborating Center for Surveillance Epidemiology and Control of Influenza, Branch Chief, Virology Surveillance and Diagnostic Branch, Influenza Division, Centers for Disease Control and Prevention. Dr. David Wentworth.

Global Influenza Virus Surveillance and Characterization — Dr. Wentworth

Dr. Wentworth: Thank you very much, Dr. El Sahly. And I'm going to try to share my screen. If you can give me the thumbs up that it's functional, that would be great. And then I am going to probably turn off my video so that I save some bandwidth.

Dr. El Sahly: Yeah, we can see your screen well.

Dr. Wentworth: Wonderful. Okay, so yeah, we're going to move right along. And so the outline for today is to cover the WHO Vaccine Consultation Meeting, which occurred for the Northern Hemisphere 23-24 season, as Dr. Weir did a nice job introducing. I'm going to spend the most considerable amount of time on the H1N1 viruses. And that's because they are a strain change for us. And I'll describe in detail only the key information to the recommendation to update the antigen for the Northern Hemisphere 2023-2024 season. I will also talk about a H3N2 viruses, as well as Influenza B viruses. I'm going to try to limit this discussion, in part because the vaccine antigens remain unchanged. I'll spend a little more time on H3N2 just to illustrate why it was not changed.

So the meeting occurred, as Dr. Weir pointed out, just a few weeks ago. It was held from the 20th to the 23rd of February. It's still a hybrid meeting. We had a couple of participants, these two, that were participating virtually from Vector Labs for the zoonotic point and from Scenic in China. Diane Wong there. And then it was chaired by Kanta Subbarao, who's pictured here next to me. And we had nine advisors that are the directors of the WHOCCs as well as the essential regulatory laboratories, like Euro FDA is one of those. And the disclosures of interest are always done at the start of the meeting. There's 39 observers from National Influenza Centers and other locations, and many experts from WHO regional offices and headquarters. And then we had an information meeting held on the 24th where we presented the data to vaccine manufacturers.

So as Dr. Weir pointed out, I'll just be quick on this slide, where they H1N1 component changed, I have here. And the confusing thing, as Dr. El Sahly already pointed out, is it's kind of funny, but it's serendipitous, I guess the Victoria/4897 is the new antigen, and it was Victoria/2405 from 2019. And actually the cell-based was an A/Wisconsin 588/2019, and it's been updated to Wisconsin/67 from 2022. So I hope to not confuse you on those points as I run through these slides.

And I'm going to very briefly cover activities so that we can spend a bit more time on the actual virological information. This slide is showing the number of positives, positive specimens for influenza, by subtype and lineage. And so you can see it was actually kind of an early peak in April here for the southern hemisphere, and then an early peak globally in from November and already dissipating down. And I'll show you this on another graph as well. And this is also showing you the subtypes that circulated. And actually, if you remember back to Dr. Grohskopf's slides, globally, we had kind of a similar phenomenon with the combination of H1 and H3 cocirculating around the same time rather than at different points in time during the season, which we sometimes see.

So to give you an idea, globally, what we saw, this is about the same numbers as for the US for the viruses that were characterized. Of those that were subtype, almost 70% were H3N2, so 69%, and 31% were H1N1. This is showing you the global distribution by country, and it's a world map illustrating where the influenza viruses by subtype and B lineage were seen between September 2022 and January 2023. And so what you can really appreciate here is that influenza A, which is the blue colors in the pie charts, predominated in most regions. And the exceptions were really like West Africa, South Africa, in some countries in Central Africa, and Central

Asia, as well as Southeast Asia and the Russian Federation, which had quite a bit of H1, which you can see there.

Alright, so we're going to get into the H1N1 viruses. And this slide now shows the number of H1N1 viruses detected by the Global Influenza Surveillance and Response System. The acronym is GISRS here. And really you can focus on the last couple of seasons, the yellow and the red, being the 22-23 time points. And you can see that we had this major increase in H1N1, really in the Northern hemisphere part of the season. And it peaked before the end of 2022 and started to fall. And you can see it coming in here into week four, where the last data was available at the time of the meeting, but continuing to fall.

And this is now a similar map, which I've showed before, but it's now showing you the percent positive specimens tested. And the key is here. The light yellow is 0.1 to 5%, and then as you get into the dark red, you get to greater than 30%. And what you can see is that it's based on these percent positives between September 2022 and January 2023. And we saw a higher percent positivity in some countries in Eastern Europe, East Africa, Southeast Asia, and a few countries in Central Asia and North Africa, as well as South America, here and here for example.

Okay, so now we're going to get into the phylogeography. So this is a very high-level view of the HA phylogenetics combined with the geographic origin, or where the virus was isolated or identified. Where the specimen was taken is a better way to say that. And it's going from, this heat map over here is showing you the years 2020 to 2023. And the phylogeny is a very dense phylogeny going down from that time point. And what we can see is, I'll just try to cover these bullets here. And those are partly there for visually impaired people so that their reader will show, will read those to them.

And so you can see, in 2020, prior to the emergence of the SARS pandemic, we had quite a bit of circulation of this group called 6B.5. And it was split into 5B, and then 5A was just starting to emerge. And then we had the Covid bottleneck where were very few H1N1 viruses were isolated. But coming through that bottleneck, five A1s continued to survive. These were in Africa for the most part in the beginning, and then they moved into Europe and Oceana, for example, and a few in South America, which is the light blue. And then there's this split here at the phylogenic tree, and I'll go into some more detail about this. And this is where their 5a.2 viruses come into play. And they've continued to evolve and split into a number of subgroups that I'll show you on a more detailed slide. So some of the key viruses here are Hawaii/70, which was the previous cell-based vaccine in the 2020 era, and Wisconsin/588, which we got this year in our vaccine. And Sydney/5, which is the vaccine recommended for the Southern Hemisphere 2023 season. And then Victoria/4897 and Wisconsin/67 down at the bottom, which are these most recent recommendations.

So as promised, this is a more detailed tree. I'll try to keep the alphabet soup to a minimum. I just want to point out a few key features of the 5a.1 and the 5a.2 that were probably hard to appreciate on that high level overview. The 5a.1 viruses. Now we're kind of at the bottom of this phylogeny here. You can see where Hawaii/70 is. This small little bar represents the 5a.1 viruses, and you can still see that there are some 5a.1 viruses circulating. So this is showing you from September through January. You can still see a few of those circulating, primarily in Africa, and a few in Europe were detected. But they’re still decreasing in proportion as we looked at them over time. And there was a couple in South Africa, South America, Oceana.

And then 5a.2. That's what you can see. I've highlighted the blue, this blue background. All of these are the 5a.2 major clade, and they've broken up now. We've broken them into sub

clades to make it a little bit easier to track. And so what we have are the 5a.2a viruses, which break at this juncture. And they're shown in this kind of salmon colored bar, which is both at the bottom and the top of this phylogeny. And in the middle of the phylogeny are the 2a.1, the 5a.2a.1 group. Okay? And so these 5a.2a viruses, they typically have these amino acid changes. Representatives of those are this A/India/PUN-NIV323546 from 2021 and A/Sydney/5/2021. And then where you get another break point is here around this amino acid changes. It's combining two different branches of the phylogeny in total. But the key point mutations are at 142R and 137S. And so you can see that these 5a.1 viruses, they typically have these 137S, 142R, and these other changes. And Victoria/4897 and Wisconsin/67 fall into that clade. And so these are, I've highlighted them as the recommendation for the egg, the Victoria. And the recommendation for the cell is this Wisconsin/67. Okay.

And I guess I should point out a couple of more features of this tree before we move on. So I showed you the phylogeny, but where they circulated, you can see over time a lot of these 5a.2 viruses you can see are just global. And it's a mixture of viruses that are 5a.2a and 5a.2a.1, with the predominant of 5a.2, a one really being seen in Europe, which is the green, North America in the blue, and this aqua color is South America. And so they were in Central Europe as well. Okay.

And then I'll show you this data later in cartography, but the final bit here is this also includes some antigen information. So the tick marks illustrate viruses that were tested. This is data from the CDC, so tested at the CDC, with ferret antisera against the Wisconsin/588 cell. And if it's less than or equal to fourfold, it's ticked on this in a yellow color. And then if it's greater than that, if it's hitting eightfold or more, it's in blue. And so you can see this kind of

binary distribution where everything we tested in the 5a.2 groups, whether it was a 2a or a 2a.1, react well with that 588 ferret antisera, and those in the 5a.1 react poorly with that.

And now I'm going to show you, so that phylogeny might be a little confusing. I'll show you what's happened to the hemagglutinin molecule as a monomer. And so on the left-hand side, we're just going to base our comparisons on the Wisconsin/588 cell. And I'm going to orient you to a couple major antigenic epitopes. So this is showing you the monomer of an X-ray crystal structure of the hemagglutinin molecule. Antigenic site SB is up here on kind of the left hand side of this face in the blue. Antigenic site SA is also at the top, and it's in this peach color. And one interesting thing is ferrets have an immunodominance feature for antigen site SA, which we're really recognizing more and more.

The receptor binding site is circled here. That's the RBS, and it's right at this kind of divot in the, so it's going down into the HA molecule in between sites SB and SA can be involved. And then antigenic site CA, which is in green. And antigenic site CB in yellow. So now if we look at the Wisconsin/47, which is a good representative of very emerging virus, probably the most divergent 2a.1, 5a.2a.1 virus. I'll call it 2a.1 in the shorthand sometimes. You can see a number of substitutions up towards the head of the hemagglutinin. Q189E, A186T, all in site SB there. E224A, which is close to the receptor binding site in site SB as well. K142R, which you can see right here. This is in site CA. And P137S, which is also in site CA. And then they have a K54Q up here. And this, we call this head part here, HA1, the top domain. And the bottom part is HA2, which is a stock domain. And we rotate it. And another substitution that's popping up in a number of viruses is this T216 A, but it's not in all of them. And it's not in the, that's the one difference between Wisconsin/47 and Wisconsin/67. Is that the 67 lacks that T216A.

So this summarizes now the ferret antigen data, and I showed you just CDC's data with the tick marks. So you can see that. And what we saw was, when we compare it to the Wisconsin/588 cell antigen.

So antisera made against that vaccine antigen, 94% of the viruses were considered within two to fourfold, which is very good. And then we start seeing some reductions, greater than eightfold, or greater at 6%. And you can see the Francis Creek Institute had a little bit higher for that, but they also were in Europe, and they also get a number of specimens from Africa and other countries around the world. So they had a lot more 5a.1s, and that's partly why they had a higher percentage with eightfold. Overall it was 90%, considered two to fourfold and 10% eightfold or more. And the egg-based Victoria/2570 did very well as well with 94% and 6%.

So now diving into just one small table that helps to make up that hemagglutination inhibition data. Here I'm showing you kind of the binary pattern of the HA clade 5a.1 viruses, which are in these first two columns and 5a.2 viruses, which are represented by this light column three and four. So this is Victoria/2570 egg virus. So the Northern Hemisphere vaccine candidates in a cell-like virus. So this is kind of the equivalent of Wisconsin/588. And you can see very good reactivity against all these 5a.2a viruses and the 2a.1 viruses, whereas the 5a.1 antisera to Brisbane and Guangdong-Maonan, which is like, you can see very poor reactivity of all these viruses even though they react well with all the 5a.1 viruses.

Now if we move to the recommended prototypes, here you have the Victoria/4897 egg on the last column. You can see that that antigen is stimulating excellent immunity and reacting very well. So the 5a.2a.1ha clade virus antisera inhibited all the recently circulating viruses very well. But we only saw modest reductions with ferret antisera to the new 2a.1 viruses.

Now when we look by cartography, that same feature is born out. And you can see, I've explained cartography to our group many times. I think you guys are really probably very up on it, but I just want to, I'll do a little level setting. Each square is worth a twofold reduction or difference in antigenicity. And what you can see here is the cluster of 5a.2, clade 5a.2 viruses. So these are viruses with HA clade 5a.2, all forming a cluster here. And these are the more recent viruses since February 2022. The older viruses are shown in gray that have been tested, so you can appreciate what that's like. And then the older 5a.1 viruses are down here. And so you can see these are forming two distinct groups of viruses that are really easy to see. And viruses in each clade cluster with the respective vaccine antigen. So here's the previous vaccine antigen, Guangdong-Maonan or Hawaii/70-like antigen. And then even the more recent virus is still clustering pretty close to that. And then we have the Wisconsin/588 cell antigen, shown here in the red, and the Victoria/2470 in the egg-shaped red. And then the new antigen, the Wisconsin/67, the new recommended antigen you're considering, shown in the purple. And so while it looks quite subtle in the ferret data, there is a little bit of differentiation here you can pick out through the cartography. That's a little bit easier to see than on the HI tables. But they're all really within fourfold of each other.

And that's really illustrated by the serum circle. So now what we're looking at is cartography that's illustrating serum reactivity of the Wisconsin/47/2022 serum. And so this is a Wisconsin/67-like virus or antisera. I showed you that HA molecule. And it's showing that if with serum like this, you really cover that whole group very well. And that circle is within eightfold. I should really point that out. So you really want that to be a little bit tighter here for really good vaccine antigen. And that's what it looks to be. But outside of that circle is where we would have more antigenic drift.

Now, one of the most important things is how does human serum react when we vaccinate folks with the Wisconsin/588 cell-based vaccine like antigen or the egg-based Victoria/2470? And so this is showing you now in a lot of panels, starting with pediatric and going to elderly. So 6 to 35 months at the top row down to greater than 65 on the bottom row. And we have a number of vaccine platforms being used here. So this is IIV4, so an egg-based and activated vaccine. And then the pediatric three- to eight-year-olds. There's Flucelvax and an egg-based vaccine. And in pediatric 9 to 17, there's Flucelvax and egg-based. And in adult, so that is 18 to 49 age group, there's Flucelvax, recombinant flu block, and inactivated egg-based vaccine. And so then we get in the older adult the IV4 again and the elderly high dose IV4.

And so now I'm going to walk you across the top of the column headers here. And so we have representatives from the 5a.2. So this is very similar to the antigen that was included in the vaccine, and that's set to 100 for the comparison of all these other vaccine antigens, or serology antigens, I should say. So the 2a group represented by that India/PUN-NIV or the Sydney/5 you can start to see just, as you get a couple of additional mutations beyond the base 2a, which is the India, you start to see more reductions. And this light orange color that you can see here on this key is where the 90% confidence interval around the geometric mean titer point estimate starts to touch the 50% line. So the point estimate's above the 50% line, but the confidence interval has at least touched it or crossed it.

Now when we get to the 5a.2a.1s, you start to see the deeper reds, where the point estimates start to move below the 50% confidence interval. And so hopefully through this heat map you can see basically all the age panels are showing more reductions as we get into the further evolved 5a.2a.1 viruses, such as the Ghana/2711 and the Wisconsin/47, which has that additional T216A substitution that Ghana and Wisconsin/67 lack.

So basically, with the exception of the youngest pediatric group, we saw reduced geometric mean titers in the 2a and the 2a.1s, to summarize here a little bit. And the other point I would like to point out, and this is kind of a nice thing to understand, the 5a viruses and 5a.1 viruses preceded the 5a.2 viruses in circulation in our population, and they also preceded the vaccine recommendation. So the previous vaccine recommendation was Hawaii/70-like or Guangdong-Maonan egg-like, and that that virus was used in the vaccine previously, and it's circulated previously. And so what you can see in these younger age groups, we're seeing not great coverage, very kind of similar to the ferrets, by being immunized with that vaccine. However, in the older, from nine to adults basically, you're seeing now blue colors back there, which means good geometric mean titers that are very similar to the geometric mean titer that's set at 100. And so this is likely a boost of memory response and sometimes called a back boost.

Now, so that was just CDC data. And this is data from all the WHOCCs and ERLs that conduct post-vaccination human serology. And I'm not going to walk you through it, but basically, we had even additional serum from the UK, Japan, and China included in these panels. And you can see that the data really is illustrating that, for the most part, all the centers agree, and that we saw reductions in these 5a.2as, and particularly the 5a.2a1s. And so what that's demonstrating is that these 5a.2 HA genes are accumulating changes in epitopes such as site SB, which I pointed out on the molecule that better escape antibodies induced by the current vaccine. And examples of that are really these 2a Sydney/5, and to a certain extent the India/PUN-NIV-like viruses. And then when they acquire the additional changes in site CA, which is the P37S and the K142R, like these 2a.1 viruses over here, like Ghana and the other one I pointed out, Wisconsin/47-like viruses, we see even further reductions, and we get to those darker reds, or

darker oranges going to red. And so that's really further reducing the human antibody recognition that's induced by the vaccine we're currently using.

And so to summarize the H1N1 viruses we have they've been detected in all geographic regions. Most viruses circulating this period expressed HA genes in major clades 5a.1 or 5a.2. And there's a variety. There's two 5a.2 sub-clades that aren't new. One's the 5a.2a, and it has these amino acid changes. They predominated in Asia and some countries in Europe and Africa. And so you can see here a phylogeny I pulled from next train, which is listed here. This is just, it's proportionally pretty good, because they do some things to decrease bias of the sequence data. And so you can see the 5a.1 here representing a smaller proportion, and then the 5a.2 breakpoint being here, being all these viruses here. And then the 2a.1s being up here at the top. And they predominated in North America and the US, for example, and in some countries in South America and Europe.

With the ferret antisera, they showed a clearer difference or distinct difference between the 5a.1 and 5a.2 viruses. And that's illustrated by this kind of phenomenon where 5a.2 antisera of Wisconsin/588 recognized all the 5a.2 viruses, including the sub-clades 2a and 2a.1, but poorly recognized the 5a.1 viruses. Also the 2a.1 virus like Wisconsin/6722 and Victoria/4897, which I showed you data on that egg antigen, recognized the recently circulating 2a and 2a.1 sub-clades well. Now with post-vaccination sera collected from people instead of ferrets with the Northern Hemisphere 2022 vaccine, which included Wisconsin/588-like viruses or Victoria/2470-like viruses, the GMTs were reduced significantly in most serum panels against most recent (H1N1)pdm09 viruses expressing the 2a and 2a.1 HA genes, and showed that the majority of recent viruses, particularly HA clade 2a.1, were escaping some of the antibodies induced by vaccination.

Just for completeness, this isn't really related to vaccine, I have this data in here because it's a good place to talk about neuraminidase inhibitors or endonuclease inhibitors. Of the 1,361 viruses tested for showed resistance in genetic or phenotypic analysis. And with the endonuclease inhibitor, baloxavir marboxil, 1,107 viruses tested, none showed resistance.

So now I'm going to turn your attention to H3N2 viruses. The similar format. This is the number of viruses detected by GISRS. Again, you can harken back to what Dr. Grohskopf showed you, particularly for the most recent season. We saw an early season of the H3N2 starting in week 38, kind of unusual. You can see where year 2021 started, where we started to have flu back after the SARS bottleneck. But its very early season peaked and started to decline and continues to decline as we move into week four, in the red line there.

This is showing you where the activity occurred, and again, the darker orange colors showing you more activity. And so you can see, based on this global map on the percent positives of all specimens tested between September 2022 and January 2023, that there was significant H3N2 activity, which is 5 to 30% positivity. And it was in several regions, including North America, Northwest Africa, you can see over here, and Europe, and in some countries in Asia and South America. So quite a bit of H3N2 activity in Europe and quite a bit in Southeast Asia.

So this is, now, I don't have a very large high-level phylogeny for the sake of time, but we've really tried to reduce some of the alphabet soup in the H3 and made additional clades. And so we've renamed these clade one. The full name is here, 3C.2a1b.2a.1 and 2. So these are the two major clades that continue to circulate, and they have evolved in the sub-clades. So clade one is shown down here on the tree. Sub-clade involved, it's 1a.1 and it's represented by this

A/Hainan virus from China. These is where these viruses primarily circulated. Nearly all were detected there.

For the clade 2 viruses, that's shown at this breakpoint here. So all these viruses are clade two viruses and they've formed a number of sub-clades, 2a through d. In the most recent six months, clades 2c and d have actually decreased. And so really what we're seeing is 2a and 2b viruses. So the 2a branch point here and the 2b viruses here. And the 2b viruses are represented by this A/Florida/57/2022. The 2a viruses have further diversified quite a bit into 2a.1, represented by the A/Maryland/2a.1b, the A/Michigan/60, a 2a.3b, a 2a.3 represented by A/Alaska, and 2a.3a, and a further mutation, 2a.3a.1, represented by A/Massachusetts. And all these clade 2 viruses show really global dissemination.

And that's illustrated here a bit. And so clade 1a.1, as I already pointed out, that's this kind of purple color, really detected primarily or only in China. The clade 2 sub-clades predominate and show global distribution. We're seeing primarily in this point of time the predominance of 2a.1b, 2a.3a.1, and 2b. And overall, the 2b predominated in this period. So the 2b is this light kind of green color. And so you can see how much of it was in North America, although we did have many of the other sub-clades cocirculating, how much of it was in South America, in Europe really globally, you can always find 2b.

So now we've talked about what these key point antigenic sites are on the Darwin/6, and then I'm showing you where changes in the various clades occur compared to the Darwin/6 vaccine strain. And again, with the light peach color being antigenic site B, antigenic site A in the green. So H3 and H1 have different nomenclature for their antigenic sites, but the, but the A and B are basically in the head again. And then these ones on the side, antigenic site E and D and C.

So a couple of the things I just want to be briefly pointing out to you is that while you're seeing lots of diversity, genetically, we're seeing some parallel evolution. So for example, this 140K, which is occurring here in site A, or on the border of it, is occurring in multiple clades. So some people call that conversion evolution or parallel evolution. And we're also seeing E50K in a number of these. And so that's a clue that the virus is really trying to escape our immunity with some of these changes. And we're also seeing for example, G53N in the 2a.3a.1 viruses and G53D in the 2b viruses. So same position, different change. Of all of these, you can kind of appreciate that the Massachusetts/18 has the most amino acid changes in the head of the HA, including one at this 96, which is different than the other ones. And that star means that asparagine to a serine would actually create a potential glycosylation signal at position 94, which also happens to be an asparagine. So NXS would be asparagine-linked glycosylation signal.

So now the analysis of these viruses by antisera to the antigens recommended for the northern hemisphere 22-23 season, Darwin/6 cell-based, Darwin/9 egg-based vaccines. You can see really quite good totals with 97% of them being covered by, well neutralized by, antisera to the Darwin/6 vaccine and only 3% being eightfold or greater. A similar phenomenon with the egg, but we do see reductions in the number of two to fourfold and increase in the number of eightfold. And that's not uncommon in an H3 egg-based antigen.

Looking at the cartography now you can see the relationship between the Darwin/6 cell and egg antigens in the cartography as well as all of these clades that have evolved and are cocirculating. So on the left we're looking at HINT data, that's high contrast imaging neutralization test, by our CC in Atlanta, or plaque reduction neutralization test by the CC in London. So both very similar type tests, virus neutralization tests, cell-based infection assays. And very similar patterns where we're getting groupings of all the different sub-clades of 2a

viruses forming one group. And the original, the clade 1 type virus, which would be the 1a.1, being down here in these older viruses. And they're not able to be appreciated here because no test viruses had that genotype for the correct data.

So now we're going to move to a little bit more data on what the serum looks like. And so here, when you look at the anti-serum to the Darwin/6/2021 from two centers, you really get a very similar pattern. The square represents the serum here, and the circle represents, everything inside of the circle, has eightfold or less reactivity compared to the homologous titer of Darwin/6. And each square represents twofold. So you can see that these are pretty much within fourfold of, and that's why 97% of them are considered reactive with the Darwin/6 antisera. And the Crick uses Stockholm/5 as their Darwin/6 like virus, but they put that antisera here. And again, two different centers getting very similar data using a similar assay.

Now when we compare some potential other antisera, say for example a Florida/57, which is one of those 2b viruses, you can see that that serum's placed here in this cartography, but we start to lose some of the viruses, their reactivity patterns. So you're covering these 2b viruses well, which are this bright orange color here, but not covering as well some of the 2a.1 viruses here. And then if we work with an antisera against this Thailand/A, which represents that 2a.3a.1 group, which may be the most evolved group, you can see it really pushes that serum circle to the right. And while you cover those 2a.3a viruses and 2a.3a.1s well, you lose coverage of some of the other viruses, including some of the 2b viruses.

And finally the human antisera shows really good reactivity. I won't walk you through. It's all the same serum panels I showed for the H1, which was very critical for the H1 information. And so I won't walk you through all that. But you can see we had a large panel of the different clades. The 2a.1a, 2a.1b, 2a.3, 2a.3a.1, the Massachusetts/18 or Thailand/8-like

viruses, and the Florida/57. These are the two most predominant groups and more evolved viruses. And then the 1a.1, which is a very different clade virus represented by that high 35. And what you can see really is good reactivity with most of these and actually very good reactivity with highly evolved. We did see some reductions, and remember, this light orange color here is where the 90% confidence interval is crossing or touching the 50% threshold line in this non-inferiority analysis.

Now to dive into that data, I'm going to show you a little bit more. I'm going to spend a little more time on this. So this is the same antigens here. And what you can see and appreciate just with two of the groups here, the 9 to 17 and the adult with a couple of different style vaccines, that if you look at their pre-titer, so against the base virus.

So this is the antigen that should be like what's in the vaccine, whether it's Darwin/6 or Darwin/9. Darwin/6, first flu cell, Darwin/9 for an egg-based. What you can appreciate is prior to vaccination, they have a geometric mean titer around 23. So if I'm looking at Flucelvax in the top row here and it after post vaccination, it goes up to 437 and the percentage indicates how many of those folks now have a titer greater than or equal to 40, which is a correlate of protection.

Now if we start going across to some of these newer emerging lineages, we're seeing that we're getting good boosting, good forward boosting, into the Maryland/02, like the 1a viruses with a GMT of 94. Michigan/60 some reduction, but GMT of 243. And 663 for the Alaska , and actually very good titer for this Massachusetts/18 and the Florida/57. And really a pretty good back boost against these 1a-like viruses. And that same pattern holds true for like the egg-based vaccine in the same age group. And then when we get into the adults, we're not seeing quite as high a titers boosting, but we're still seeing really good change from pre-vaccination to post-

vaccination. And you can see that in each of the columns here. So a pre-vaccination titer against this advanced Massachusetts/18, 15 jumps to 243, for example. And with the FluBlok you can see a higher titers were achieved in that case.

So what did I want to tell you here? The antibody titers increase to all clades, which I just walked you through. In particular the 2a.1a, the 2a.1b, and the 2a.3a.1, which are all increasing. And we did see good but smaller increases in the 2b, which is this Florida/57. So you can see like 320 versus 394, for example, in this group. Alright.

So I know you like to see some of the individual serology, so I added that. So the in many countries, so to summarize the global circulation and phylogeny, we had reporting of Influenza A viruses and H3N2 subtype predominated in almost everywhere. There was significant H3 activity observed in North America, Northwest Africa, Europe, and some countries of Asia. The phylogenetics of the HA, of the viruses circulating this period, belonged to two major cades, the clade one, and that's evolved into the subclade 1a.1 which has this I48T and K197N substitutions. And they were detected primarily in viruses circulating in China. And the clade 2, which has global dissemination evolved into kind of medium size clades, the 2a through 2d. And the 2a have further evolved into multiple sub-clades. And the 2a.1b, the 2a.3a, and 2b have predominated in this reporting period.

So viruses expressing the clade 2 HA genes included subclades that are energetically closely related and are energetically distinct from the 1a.1 viruses. And so that was the big gap you saw between the one 1a.1 virus I had on the cartography from the CDC. Comparing antisera to Darwin/6 recognized all the clade 2 viruses, whether they're, and all their sub clades very well. With one, the virus is expressing the 2b, showing some subtle reductions in reactivity. But they had poor reactivity to reduce reactivity depending on the collaborating center that did the studies

with the clade 1a.1 viruses. For Florida/57, which is a clade 2b virus. It recognized its group well but showed reduced recognition of other clade 2 sub-clades. And similar was true for the Thailand/8 and Massachusetts/18-like viruses, which are these 2a.3a.1 viruses. They recognize their clade very well but show reduced recognition of the other two sub-clades.

For the human serology with serum panels from individuals vaccinated with Darwin/6 or Darwin/9-like viruses. Most of the human serum panels reacted well with recent H3N2 viruses that expressed diverse clades and sub-clade HA genes. We did see that panels from some of the younger age groups showed reduced reactivity with viruses expressing the 2b or the 1a.1 HA genes. And for the antiviral susceptibility, we're in good shape with the H3N2 viruses. Over 2,600 were analyzed, and none showed genetic or phenotypic evidence of reduced inhibition to neuraminidase inhibitors. And the same is true for 2,429 viruses when they were analyzed for susceptibility to endonuclease inhibitor baloxavir marboxil.

So now I'm going to turn our attention to the Influenza B viruses. Here we're looking at the B viruses detected in 22 and 23, and you can see it's relatively low circulation of influenza B. We did see an increase around the same time where we started to see H1 and H3, and it's kind of continued on. And it hasn't fallen as fast as we've seen for the H3, I would say. But it's just staying at this very low level. So for circulating Influenza B virus lineages, we talked about this almost at the outset with some questions. Of the viruses were lineages were determined. All of them were B/Victoria. And so that's a bunch of them were b lineages and were unable to be determined in the global scene.

Again, now looking at the activity from September 2022 to 2023, we did see some countries with a percent positive specimens of all the tested had 0 to 5% positivity. So many, many countries had that yellow, which is this kind of light-yellow color. And some countries had

quite a bit more. So for example, in South America, in North Africa, in Central Africa, and in parts of Europe and Southeast Asia. So looking at the B/Victoria viruses. Here's the genetics again. The layout is the same as I described for the H3N2 viruses.

The 1A.3 viruses. So those are down here at the bottom of this phylogeny and represented by this like B/Kenya/186 here. They've derived from older viruses that were more have more genetic relationship to the B/Washington/2/2019 vaccine virus. But they have a few, just a few additional substitutions. And you can see we still have a few of those circulating, and they were primarily in South America and a few in North America. But the majority of viruses are these 3a.2 viruses. So V1A.3a.2, and I'll call them 3a.2 viruses for shorthand. And that's where the B/Austria/1359417/2021 vaccine antigens for cell and egg sit, right in the smack middle of that phylogeny. And then we have a couple of viruses used that have a few changes such as this D197E, which is an interesting change that we're seeing in Asia and the Americas, representing that, that we'll use in serology. As well as this B/Maryland and a B virus from China as well. Okay.

And so what we're seeing in these 3a.2 viruses is a global distribution. You can kind of tell that by the color coding of the tick marks you're seeing here, and a lot of that circulation in Europe, which is the green, with, they continue to diversify. And this H122Q virus is really kind of like this virus here. The 182, 197 and 221 in North Africa, Europe, and North America. So we're seeing those viruses more often there. And the 197E alone. So we're seeing that parallel evolution at the 197E. So here's the 182, 197, and 221, and here's the 197E alone. And so we have representatives of those that will show up in the human serology.

For the global clade diversity, this bar graph is just looking on based on HA sequence availability solely. But you can appreciate pretty easily the reduction in the V1A.3, and 3.1 over

time, and the increase of these 3a.2 viruses globally. Okay? And so this is from September 21 to January 31st 2022, and then Feb to August 2022, and then September to present 2022.

What you can see here is the sum total of the antigen analysis. Remember, B viruses weren't in huge circulation, so there wasn't as many to test, but 99% of them are considered reacting very well within two to fourfold of the cell-based vaccine antigen. So ferret antisera of that, and ferret antisera to the egg-based cultivar of B/Austria also reacting really well, 99% less than eightfold. So two to four-fold would be another way to say that.

Now, looking at the cartography, I've kind of overlaid the serum circle and the cartography for brevity, but what you can see here is the clustering of all these kind of sub-clades of the 3a.2s that have potentially the 122Q or the 197E really antigenically overlapping with each other and very proximal to the cell- and egg-based antigens. And so that's showing you the serum circle for the cell-based and the serum circle for the egg-based on the right. Both of these are from the CC in London.

Now looking at the human post vaccination serum analysis of the B/Victoria viruses, you can see these are all 3a.2. So I didn't put a box on here, I thought I did, but I'll highlight it with my red pointer. All these represent 3a.2 viruses and this Austria vaccine-like virus that's been used is inducing antibodies that well recognize all these viruses. We do see reduced recognition of the Washington 2 and V1A.3 viruses overall. And that's to be expected. And part of the reason the Austria was selected over the Washington was the antigenic distinction between those groups. And we're seeing continual decline of these viruses here.

So this shows that the current vaccine antigens elicit antibodies that well inhibited the majority of recent representative B/Vic lineage viruses from the 1A.3a.2 sub-clade. And this included some that had some additional amino acid substitutions, which are listed above there.

So to summarize, on the B/Yamagata situation, there have been no confirmed detections of circulating naturally occurring B/Yamagata/1688 lineage viruses after March 2020, and including this period. Recent reports of B/Yamagata detections could not be confirmed as naturally occurring B/Yamagata lineage viruses, or were identified as B/Yamagata lineage component of live attenuated vaccines. And we cannot yet be confident that B/Yamagata lineage influenza viruses are extinct. The GISRS, the Global Influenza Surveillance and Response System, will continue to actively conduct targeted surveillance for Influenza B/Yamagata lineage virus.

So to summarize, really, the B/Victoria situation, we only saw B/Victoria lineage during this period. There was not a huge amount of B virus detections in general globally. The phylogenetics of the HA, we still see a few 1A.3 viruses, these descendants in North and Central America. It really represents 1% of viruses collected since 2022. And B/Kenya was a representative. The 3a.2 predominated and have global distribution. They share this A127T, P144L, K203R, and B/Austria/1359417/2021-like virus represents that group. They continue to diversify. The post-infection ferret antisera raised against the B/Austria component well inhibited all the 1A.3a.2 viruses, which predominate, and poorly inhibited the 1A.3 Viruses, which continue to decrease.

For human serology and antiviral susceptibility. With the human serology studies, and I just gave you that high level, all the CCs and ERLs combined view, really illustrate that the recent representative B/Victoria lineage viruses from the 3a.2 subgroup were well inhibited by all the serum panels. We did see significant reductions in the geometric mean titers with most serum panels for viruses from the 1A.3 clade. And for antiviral susceptibility, none of the viruses showed reduced susceptibility to neuraminidase endonuclease inhibitors. Thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Wentworth, for your biannual updates on a very complicated topic. And you lay it out so clearly to all of us and to the public. I invite the committee members to use the raise your hand function to ask questions to Dr. Wentworth. And we begin with Dr. Offit.

Dr. Offit: Right. Thank you, Dr. Wentworth, for a very clear presentation. I want to get back to a question that Dr. Portnoy asked and that Dr. Grohskopf answered and then deferred to you. So for example, last year when we picked strains, we thought we did a pretty good job of predicting what would be coming into this country. Nonetheless, we had whatever, 60 plus percent protection against severe disease against for hospitalization in the pediatric age group. Dr. Grohskopf, when she answered the question that he asked, alluded to the fact that this may just be, that we're looking at a drifting virus. And so is it fair to say then that this virus doesn't just drift, for example, from one year to the next, but drifts more frequently than that, so that we can only do so well at predicting strains? And so we therefore wouldn't expect to do any better than what we've just done? Thank you.

Dr. Wentworth: Thanks, Dr. Offit. Yeah, it's an interesting question. And so I think we have to, I'm going to try to be very clear here, because there's genetic drift, which flu does almost faster than almost any other virus, and it does it at a population scale. So it's really challenging from that perspective. And I think one of the things we have to understand that I think is important, is not necessarily always predicting the perfect. And then there's, let me just finish that first statement. Then there's antigenic drift, which is this more significant, how many amino acid changes do you need to really push it over the edge and push it farther and make the virus

able to evade prior existing immunity from infection or vaccination? And that's the more important kind of drift that we're talking about.

And when people sometimes use the term match, which portrays flu as a black and white situation, which is not true at all, it's a lot of shades of gray. And so it oversimplifies the situation. So you're right, we're just. During a season, we can see drift occur during a season that happens all the time. It's very subtle. Like I showed you with the 2b viruses, those are going from right at the edge of our ability to recognize drift. So twofold, reductions. You can't see more than, fourfold is a very accurate, oh, I know it's different if it's at least fourfold different nonhomologous titer. And then eightfold it's clearly different, but eightfold by ferret antisera really only is less than twofold with human sera. And that's why we use this 50% cutoff with the human sera.

So we we're kind of mixing a lot of things here. When you use a naive ferret animal model, they're very exquisitely sensitive to point mutations on the hemagglutinin and really can help us identify drift earlier. And that's why ferrets are important. And then with the human response, we have all that prior infection, and we have a broader response, even I think as naïve, that needs to be worked out more. But we have a little different response, and you can clearly see that with the H1 viruses in ferrets.

And so when you have that all happening now, the other side of the coin is really a high bar of protection from infection with vaccine effectiveness estimates using a test negative study design, right? So you have, there's many factors there besides how well the vaccine induces sera that neutralize the virus, right? That's the thing that I can look directly at, and I showed you data directly on. So we can look at that data and say, yes, we are inducing sera that recognizes the

virus. But how high those titers are differ between different people and differ between different vaccine seasons even. And so you can get that titer problem.

You can also have, what's your negative control group and how much have they been exposed to flu in the recent past? Or how, were they vaccinated in the recent past but not vaccinated this season? And that, I think, confounds the data a bit. And so I think it's extremely challenging, and I think Dr. Grohskopf answered. I'm not the VE expert that she is. But there is a lot going on in real world vaccine effectiveness estimates, and they're not efficacy estimates. And I think even with SARS, this panel, I think many of this panel is on the VRBPAC for SARS. You can see what a high bar it is to protect against respiratory infection. So that is a high bar to meet, to have an immunity that's going to protect you from infection and symptomatic disease.

And then to your question about more severe disease like hospitalization, that question. It's very difficult because why someone is hospitalized in an older age group can be for a lot of reasons that aren't really a severe disease. And so I think we need a slightly different, I don't know how to do it. And I leave it to my colleagues at the CDC to do VE against more severe disease. But it's challenging to do, because you can't really use hospital admission, because many people will be admitted just to be precautious because they have flu and they're in an age group or they have other comorbidities that might be a problem. So we don't want that to go the wrong direction.

Dr. Offit: So it boils down to one of two things. Sorry, just one quick follow up question, Hana. It boils down to one of two things. Either one, I guess is how we define the word drift. I mean, there's drift has a more specific meaning. Maybe there's sort of like drift-like, or drift-ish. There's some somewhat of an evolution,

Dr. Wentworth: Yeah.

Dr. Offit: But not a dramatic evolution. And then the second thing is, I mean, you're alluding to something I hadn't really thought about. Certainly this is an issue for SARS-CoV-2, are those hospitalizations and ICU admissions and deaths really for Covid or just with Covid? And you're saying that's also an issue here. So you think both things are going on then?

Dr. Wentworth: Yeah, I think both things are going on. I'll be over-simplistic and state that. And I just think that, yeah, I think it was a great question by Dr. Portnoy, but I also think, and it's great to want to achieve a 90%, but some of the things that you see that high, high VE in are very different. They're not acute, really fast respiratory infections like flu is and like SARS is. But flu being faster than SARS as far as its replication speed.

Dr. El Sahly: Thank you. Thank you, Dr. Offit and Wentworth. Dr. Pergam.

Dr. Pergam: Hey, Dr. Wentworth, this is Steve Pergam from Fred Hutch in Seattle. I just want to get back to the Yamagata strain, sort of the elephant in the room here. What is it, from WHO and others that are in this committee, what is it going to take to sort of decide that it's done? I mean, there's a sort of worry that it might come back. We have had two years without any Yamagata really detected. I mean, obviously it's a different season with Covid, but might there be an opportunity to have maybe a second H3N2 or some other component that might be beneficial in terms of providing broader protection against strains that we know are circulating? So, I'm curious if maybe you could talk a little bit about what is going to be the threshold for potentially Yamagata strains being removed.

Dr. Wentworth: Yeah, I mean, this is a real challenging situation because there's a few things that we need to consider there. There hasn't been a strong Influenza B season since SARS emerged, so we really haven't had like a very large Influenza B season. And so that's one of the things. So time is a piece of the factors. You know, unfortunately it's going to take time, but as

Dr. Jerry Weir pointed out, there's no vaccine that you could put two H3s in that's licensed yet. So, I mean, I think they're two separate questions. I really, I think it's laudatory to think about new vaccines that will improve the effectiveness of protecting people from infection and serious disease, et cetera. So that's a good opportunity.

But with B/Yamagata, there's that piece of the puzzle. One of the things I pointed out at the last VRBPAC when we got into the Yamagata discussion was if you looked at H1s, we didn't detect any 5a.1 viruses for quite a while. And then once SARS subsided a bit more and we got into later stages of the pandemic, we saw that virus come back. And it looked a little bit like it was gone. So there has to be a more concerted effort and we've been trying to really support all the GISRS labs to do more lineage typing. So there's still too many viruses that go just as typed as B, but they aren't lineage subtyped because that's an extra test that has to be done. And so we'd like to see a lot more data in that space as well. So it's kind of a combination of time.

And then the third element that will be discussed at some point in time, within at least the WHO community, is what is the real risk that B/Yamagata would represent? Even if you can't declare it extinct yet, what's its risk level? And so that's, I think, a thing that you might be driving at as well.

Dr. El Sahly: Thank you, Dr. Pergam and Wentworth. Dr. Monto.

Dr. Monto: Well, I may surprise you by not, Dave, by not bringing up why doesn't industry start looking at the possibility of 2 H3s, let's say, in the vaccine? Because unless they do that, we don't have a good alternative for switching out of the B/Yamagata quadrivalent. But I wanted to move back towards the question of egg-based versus cell- and now recombinant-based selections. It seems to make a difference in what you showed only for H3. Yet we have different strains selected for everything, even for B, which has the same designation, but is a different

isolate or different cultivate. Where are we now in terms of moving towards something where the recombinant at least reflects the best? And is the cell culture-based strain still the best in terms of FIT, or whatever you want to call it? And where are we now with all the different laboratories working on this towards getting a better cell-based?

Dr. Wentworth: Yeah. Okay. So that's you always, you're great, Dr. Monto, you always ask me challenging questions. And so this is really, what I'm here to do is present what the data is on antigenic drift and the vaccine selection. But I'll try to touch on this. So, we've moved, I think, in good directions, both in the WHO Vaccine Consultation Committee Group and the VRBPAC in really specifically stating which viruses are for egg and cell. Those used to be a little bit harder to determine. Now we have accession numbers for the sequences if you go to the vaccine recommendation page. So somebody that's trying to develop a new cell-based vaccine or a new recombinant vaccine, whether that's recombinant protein or nucleic acid, could use those sequences to develop that particular antigen if they so choose to go after it.

For the egg-based vaccines, what we understand very well is that in each of the viruses that we propagate in eggs, they have to undergo some adaptation to replicate efficiently in eggs. And the efficient replication is critical to make millions and millions of doses of vaccines. So it's the combination of the first egg adaptive changes that happen, and then the reassortment, often for at least Influenza A viruses with high yielding backbones, that really allow us to vaccinate so many, many people. And egg-based vaccines still, as you kind of indicated, predominate in the market, both in the US and globally. And so it's a key antigen. And so with, for example, with Influenza B, the adaptive change may be quite subtle. One amino acid near the receptor binding site. Same is true lately. When we are selecting egg-based vaccines, we are looking at those that have the least antigenic impact. So amongst all the egg isolates, we look to see which ones react

most, like cell isolates, right? And so that's part of the analysis that down-selects various egg prototypes from being nominated.

Now, as you clearly identified, H3 is the most challenging. It's very human adapted to the human 26 receptors. And it does not grow as well in eggs, which have these sialic acid with a 2-3 linkage to galactose. And so it generally has to undergo two to three substitutions rather than just one in order to replicate efficiently in eggs. And so that's why even with the ferret antisera I showed you with the Darwin/9, which has a pretty good phenotype as an egg virus, we do see some more subtle reductions that push it beyond fourfold, reduced from the twofold that we would see with the Darwin/6-like system. The various new vaccine platforms can address this issue, and it does to me look like it could potentially help with match. But there's other factors, that I think Dr. Grohskopf kind of alluded to, in the real world setting that I don't think we fully appreciate when we get down into the real nitty gritty and granular using a ferret. You see one thing. And it may not be as reproducible in humans where you get a broader response and whatnot.

And part of it to me also is the magnitude of the response you get. So you could have a perfect antigen with a low magnitude response, it still won't protect you very well as an imperfect antigen with a very large magnitude response. And I think that, I'm not sure how that differs between the different platforms other than with the FluBlok, it has 45 micrograms of antigen in it. So it's basically similar to a high dose egg-based vaccine, where that has 45 micrograms instead of 15 that's required to be in the Flucelvax and regular inactivated egg-based vaccines.

So I think it’s like I've said with other things. It's kind of complicated by the different styles of platforms. But the true issue for us is when we isolate viruses in eggs, which is required

to propagate it, and that, for that platform, it almost always has to change. And the changes are, tend to be more subtle in the H1s and the Bs.

Dr. Monto: Are you still having problems getting cell culture-based vaccines that are grown in acceptable cell lines?

Dr. Wentworth: Well, not really. I mean, with Flucelvax, they have the qualified manufacturing cell line, which has a very long name, and I cannot remember it, but it's derived from MDCK cells. It's like P30-something. And that cell line, so for example, our collaborating center has an agreement to use that cell line for virus isolation. And so we use that to isolate viruses that are in each of these clades as they emerge as potential vaccine candidates. And so does the collaborating center in Melbourne. And so they're doing it as well. And so that is helping to provide seeds for the cell-based manufacturing.

Dr. Monto: Thank you. Complicated topic.

Dr. El Sahly: Thank you, Dr. Monto. Dr. Janes.

Dr. Janes: Thank you. I have two questions, if that's okay, Hana. So my first question is, I guess, just a bit of education. So for the human serology analyses, so the serum is taken from individuals vaccinated with the previous year's vaccine, as I understand it. And I'm wondering what do we know about those individuals' infection histories? I assume not much. And if so, I'm wondering would one learn something about studying inhibition, not just with vaccinated persons' serum, but also with individuals who are known to have had previous infection in the previous years, especially in years where there's quite a burden of infection over the previous year.

Dr. Wentworth: Yeah, so we don't have a lot of data on those participants. We just, we work hard to get participants in that represent a variety of vaccine platforms. And we don't have

a lot of data on whether or not they were vaccinated the year before, whether they were infected the year before, those kinds of things. I agree with you. A lot could be learned from that. That gets a bit into kind of some more research that could be done on what prior exposure histories would, and how they impact maybe the optimal vaccine choice.

The best we can do at this point in time is with the age groups. This is one of the reasons we have so many age groups now. This is not a, it's an extensive amount of work that has to be conducted in a 'just in time' way with all those serum panels that come in. Just because people are just getting vaccinated in November and December, so we're collecting sera from those folks and getting the data for this meeting. And so the younger age groups, they offer at least an inkling of likely no prior infection or prior infection or no vaccination prior.

So like for 0 to 36 months old, all those participants haven't had a prior vaccine. So we know that, for example. We can't guarantee they haven't been infected before. One way, if we're concerned about that and biasing our data in some in some way, we can see from their pre-immune sera that maybe they're higher titer than the other people against a particular group of virus. But that's pretty difficult to narrow down. So it's a great question. But I think it definitely is in a little bit of a research realm as to trying to understand what the benefits of your first exposure are, what the benefits or negatives of different exposure histories over time.

Dr. Wentworth: Thank you. And my second question is asking I guess for a bit of speculation. I wonder if you or Dr. Grohskopf could speculate about the early peak in the flu season this year. What is that hold for us in terms of the dynamics, the temporal dynamics, for the coming season?

Dr. Wentworth: Yeah. Well, I'm happy to speculate on it. I think in general we had a lower-level immunity against H3N2 in particular, but against flu in general, in part because of all

the non-pharmaceutical interventions that were associated with SARS, and then potentially viral interference associated with SARS-2, which the COVID-19, the agent for COVID-19. Right? And so overall, I think all the populations had a little bit reduction in their prior infections over the last couple years. And so the other problem with influenza, and it gets into the vaccine effectiveness discussion, is our immunity to the virus from previous infection wanes very fast. Our immunity from vaccination wanes very fast, so it just keeps decreasing as time goes on.

And so my feeling there is there's a bit of reduced population immunity. And then the reemergence of the H3 at a time when people were now feeling like, oh, I can go out and I can have dinner, and I can, we're coming out of the pandemic. And a lot of the non-pharmaceuticals dropped off globally in around the same timeframe as well. So that spurred these viruses, you saw RSV kind of do the same thing, an earlier season with RSV than usual and a more significant peak. I cannot for the life of me even hazard as to why the peak dropped so rapidly, and that did that in multiple countries. So it peaked early and then it also declined rapidly. If all that I just told you was true, you may expect that it would continue to just stay at a high level for a quite a while. So I'm clearly not right.

Dr. Janes: Thank you.

Dr. El Sahly: Not, partially right. I mean, it's not, I wouldn't discount that. But anyway, Dr. Berger.

Dr. Berger: Thanks. I actually have two questions as well, and I think one of my questions is actually for Dr. Weir, so I'll ask that second. But I was looking back at the data that you presented and thank you very much. This is a really great talk and it makes the data very easy for us to follow. The neutralization slide that you put up for H3N2 specifically showed a difference between 3- to 8-year-old pediatric populations and pediatric populations that are 9 to 17,

specifically in relation to 2a.1b reactivity, or sorry, neutralization. And I was wondering what might explain that difference or what kind of hypothesis you might have between the difference there. And I apologize, I don't remember what the check with the light blue means compared to a darker blue, but yeah.

Dr. Wentworth: I probably neglected to explain it this time. So the check means that it's statistically significant data. If it has a plus, it means that the geometric mean titer of the virus that we're comparing to, so for example, in that case, the Darwin/6 or Darwin/9-like homologous titer would be very low. Like if it was 40, then you don't have much linear resolution. And so even if it's like, say 30 geometric mean titer comparison, we would have like a plus mark in that blue and orange graph. And so you've got a good eye.

What you were picking up on there is some reduction. So in the pediatric 6 to 35 months, the antigen was quite good in that it protected against all the 2a subclade viruses. So that clade 2 and all of its subclades. Where it fell off in that age group, and it's still protected to some extent, but we had that orange coloring, which means the 90% confidence interval was touching our 50% threshold line, is the 1a.1 virus. So that's an antigenically very different virus and almost would be, I would've expected in that age group that it would've been even more distinct. Like it would've been burnt orange or closer to the red color. Because that age group is more similar to a naive animal model age group.

Now, then, I think you picked up on a couple of other things. In the older pediatric panel, we saw a similar feature in the two older pediatric panels with the Florida/2, that 2b group, they were subtle reductions again from the 3-year-olds all the way to the 17-year-olds. So that represents like four panels, because there's Flucelvax and IAV4 in the three to eight and Flucelvax and IAV4 in the 9 to 17. And so it's really only in a couple of those panels. But what

you're seeing there is, again, some touching of that 50% threshold, but not crossing. The point estimate didn't cross it.

And the other thing that we were happy with is that the raw geometric mean titers were quite high in the hundreds, like couple hundred, 300. So, even though you're trying to compare it against that 50% threshold, that's a pretty good titer, and it likely explains why that VE that was presented actually is pretty good VE for H3N2 viruses. So I'll just put in context what Dr. Grohskopf put in play, because that's also in consideration in the vaccine consultation meeting, is that the VE against H3s can be much lower. And so that wasn't a bad VE.

And there's other studies, one published in the MMWR by the by the group out of Milwaukee, the Marshfield Clinic group, where it ranged from 60 to 70%. They had a very early and strong season there. And most of that was H3 for that age group, for that same window, from like under 18 kind of age group. So the \ VE in that case, the vaccine estimates with test negative design kind of mirrored a bit with what we're seeing with the serology. We had a lot of 2b viruses in the United States, and we had pretty good VE for H3 in the United States.

Dr. Berger: Thanks. That is actually helpful. And I think the VE for what, 6 months to 17 years old against hospitalization was 68%. So I suggest that maybe even these numbers are still somewhat protective, at least. So thank you. That's really helpful for understanding the data.

The second question, like I said is maybe more directed towards Dr. Weir. But you know, it was a comment that you made in terms of the ability to actually approve a vaccine right now based on the current licensure. And that right now all the licensure is actually going to have to be the 2A's and 2B's with that B/Yamagata strain being the fourth. And I guess the question is, because Dr. Weir pointed out that we actually need a specific recommendation to make a change along those lines. But the questions seem to be missing that, I mean, if we have to approve a

vaccine today that is a composite of what's actually in the licensure versus putting out a message that says we want to start looking at a potential change to what one might suggest being a third A strain. You know, are we missing a question that that should be posed to the committee along those lines?

Dr. Weir: Hi, Dr. Berger. I don't think you're missing anything. It is sort of a bigger issue than what we're addressing at the committee today. I think, I guess I've said this before, I think any sort of move toward a different composition than what we have now really does need to be globally coordinated somehow. And so it probably should start with, and again, I'm not trying to pass the buck, but I really do think this should probably start with discussions at the WHO for how, globally, manufacturers would respond to a change in environment where really one does not have a B/Yamagata and where one might could do something else that is more in the interest of public health.

So, of course this committee is free to make suggestions and what they think should happen. We would welcome those. But I do really think that this is a global issue that needs to be addressed, and probably a push from the WHO as well as individual countries to encourage manufacturers to generate data that could be considered by the WHO, as well as the VRBPAC in future meetings, that would support some different composition that might be advantageous from a public health point of view. I don't know if that answers your question or not. But again, I don't think we're missing anything here. I think we've noticed this. Others have. And my impression is from talking to the chair of the VCM of this most recent one is that the WHO does intend to address some of these issues over the next year or so. At least that's what I was told, and I hope that's the case. David, do you want to add anything to that? Over.

Dr. Wentworth: I don't think I do want to add anything. I mean, we are basically trying to work hard to figure out and address more about Influenza B and make recommendations as a WHO committee. But as Dr. Weir said, even if we made a recommendation, it really matters on what the license is. And this is an area where I don't have expertise, and FDA does. That work, as Dr. Monto kind of started us off with in the questions for me, needs to be accomplished.

I think, I'll just state scientifically, that it's easy to think two H3s would be a good thing. So we'll use H3 as an example. We've got two diverging clades that are both happening. And what I showed you was Darwin/6 . Antisera covers both those clades better than either of those clades cover themselves, than either of those clades cover the other one, right? So they're diverging from a point and they're closer to that point that they're diverging from than they are to each other antigenically. Okay. So one could consider, let's put both of those in the vaccine, and in some ways that might work. Say for example, position 140, where they have convergent or parallel evolution and they both, and that's in site SA, you know, site NA. And so then for that particular epitope, it would almost be a good thing to have double the amount.

And then, but a lot of people think, so when there's, often we have non-parallel evolution happening. So just diverging evolution, that if you put both those in the vaccine it may not give you the prime against both of those antigens, and that's what needs to be tested in animal models and humans to me. Because what it could do is highlight the conserved epitopes between both those. That is basically double the amount. And so you create immunodominance not at the place that's under the strongest evolution. You create immunodominance where there's conservation. And that that may be fine. That may be a great thing. Or it may be a negative. Right? And it kind of gets into some of the questions that, like Dr. Janes asked, in prior immune history and what

that would do. So it's very convoluted and it's, I think it's overly simplistic to say, just put two in there without data.

Dr. Weir: Yeah, I think you're making a strong case for the need for data for decisions like this, of course.

Dr. Berger: Which is actually what prompts the question and whether we're missing a question that would enable the manufacturers to start developing that evidence. Because I agree. It'd be nice to be able to see what is going to be the most effective combination here. But it raises questions about whether they could actually develop those additional vaccine types in order to start testing for the fall, for instance, where you able to have those preclinical models running between now and fall, and those are ready.

But I mean, that's part of the reason I was asking the question, are we missing one that would allow for that prompt? But I understand where you're coming from in terms of trying to have this be globally coordinated, so, thank you.

Dr. Weir: Yes. And can I make one more point about the global coordination? Remember, these manufacturers produce around the world, and that's also part of the reason why I stress the global coordination here. But back to your question about are we missing anything, I think that maybe if I can make a suggestion, maybe after the end of the voting, when usually there's a chance for the committee members to make final comments, maybe that would've be a good place for you to make comments like this for the record. Over.

Dr. El Sahly: Thank you. I think some of these comments also were made on the last meeting, but. Dr. Wentworth, you will be back after the OPH, right?

Dr. Wentworth: Yes.

Dr. El Sahly: So we have an opportunity to ask questions because I have, and I'm sure many others do. But we have a break scheduled now. 10 minutes. It was a 10-minute break. We cut into it, so it's now seven minutes. So let's reconvene at 12:30 Central time. I'm sorry, 12:30 Eastern time.

DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness — Dr. Fries

Dr. El Sahly: Thank you all. We will be reconvening now to listen to the presentation by Dr. Anthony Fries, the DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness. Dr. Fries is DoD, Global Respiratory Pathogen Surveillance Program Lead at the United States Air Force School of Airspace Medicine. Dr. Fries.

Dr. Fries: Hi everyone. My name is Anthony Fries, and I'm here today representing the DoD's Defense Health Agency. I sit in the Defense Centers for Public Health Dayton, which resides at Wright Patterson Air Force Base in Ohio. I'll be presenting the results from various DoD influenza public health efforts from multiple partners. Next slide.

I'll touch on a number of things today. First, an overall description of DHA surveillance efforts. I'll then present data on the mid-year VE estimates from two distinct studies here within the DoD, one estimating influenza VE in DoD healthcare system beneficiaries or dependence, excluding active-duty members, and a second study examining VE in-service member populations. I'll then provide a brief summary of some phylogenetic diversity and antigenic characterization for the isolates we've obtained in the DoD this flu season. Next slide.

So, influenza surveillance is part of several large public health initiatives throughout the DoD, many of which are led by DHAs Global Emerging Infections Surveillance Branch, or GEIS, which sits in the Armed Forces Health Surveillance Division of DHA. These surveillance

programs extend over 400 locations in over 30 countries. In addition to monitoring US military personnel and their dependents, we facilitate public health relationships with foreign entities as well as local nationals. And this work is essential, as we really closely monitor our active-duty military personnel for respiratory illnesses like influenza. And in turn, we utilize these health encounters for various reports, studies, and analyses like I'll be sharing today. Next slide, please.

As mentioned, the surveillance network is spread across all six what we've termed 'combatant commands', with multiple laboratories within these regions. When organizing these annual activities, we often take into account where we have interests as well as where WHO efforts are located. Next slide.

Additionally, our surveillance can significantly contribute to regional WHO surveillance. So you can see some DHA-funded efforts in Ghana shown here in the top panel, just representing some influenza activity in the country, while in the bottom panel, the WHO Flu-NET data, aggregated influenza activity in the region. Just to exemplify how our DoD efforts can provide a significant contribution to regional testing efforts and sometimes can be a considerable source of those data for a region. Next slide.

So now I'll jump into the actual data with the background covered. We'll transition to our first set of data. We'll go into the mid-season VE estimates from healthcare beneficiaries, excluding our active-duty component. Next slide.

So this dependent or beneficiary investigation was conducted by the Air Force's School of Aerospace Medicine here in Dayton, utilizing the DoD's Global Respiratory Pathogen Surveillance Program, which leverages an infrastructure of about a hundred sentinel surveillance sites, heavily concentrated in the United States and Germany, and really in Europe all over. And this program requests systematic sampling of about 6 to 10 ILI encounters, influenza-like illness

encounters, weekly from each installation for subsequent laboratory testing. And this is a test negative control design, and cases included specimens testing positive for influenza by PCR and or viral culture. These data were gathered from between October 2nd through February 18th. And to preempt the impending question of RSV or SARS-CoV-2 testing, negative as sort of criteria for inclusion. Those were not considered in the case inclusion in this study. Nor in the next one.

The case definitions for ILI presentations use three different approaches of fever and cough or fever and two additional symptoms shown here, or a physician diagnosed ILI. And these details are gathered from questionnaires collected from our partners at each patient encounter. And additionally, any vaccination registries and healthcare records are used to confirm vaccination statuses. And so in this study, we are estimating VE against medically attended, symptomatic, laboratory-confirmed influenza infections in an outpatient setting. Next slide.

Controls were matched based on age and collection dates, and we conducted four analyses estimating VE against Influenza A infections in children, adults, and all of the dependents, so both age groups. And additionally we estimated a VE estimate for a subtype specific H3N2 for all dependents, as well. Next slide.

Some things to note about our cases. A little over 50% of our cases and controls originated from encounters in Europe, to note, and particularly from the Landstuhl Regional Medical Center in Germany. In all, we had 240 cases and 960 controls with vaccination rates of 47% and 58% in those groups, respectively. To be considered vaccinated, an individual needed to present 14 days or more after receiving the 22-23 Northern Hemisphere vaccine. And if you look at the figures on the right here, you can see our subtype distribution for these cases, with the majority of subtype cases being H3N2, and a large portion of our European cases were not

subtyped and remained un-subtyped, to note. But the lower number of H1N1 cases ultimately prevented us from calculating a subtype specific VE estimate for H1 here. Next slide.

A few key demographic features to note. There was no significant difference in cases between males and females, but this population does skew towards younger age groups, with about 74% of our cases occurring in children 17 years or younger and only 12 cases actually in the 45- to 64-year-old age group. And lastly, 80% of our cases occurred in November and December. Next slide.

On this slide, I'll just stop the highlight that we calculated both crude and adjusted, with adjusted accounting for age and geographic distribution. However, I'll focus on the adjusted VE estimates on the next slide. So, next slide please.

As a reminder, we calculated four estimates of VE against medically attended, symptomatic influenza infections. This first is the adjusted VE against all Influenza A in dependents. This estimate was at 49% and was significant. Secondly, the estimate for VE in children was estimated at 45% and was significant. Our adult estimate for VE against all Influenza A was 44% but was not significant. And we did have the power to calculate VE against medically attended, symptomatic H3N2 infections, with a 65% estimate in our overall dependent population, which was significant. And so, to note, when we included children from 6 months to 2 years, we added another 18 cases, and our estimates moved up by about five percentage points each in all of these analyses that included children. And to note after the conversation that Dr. Wentworth had, these H3N2 VE estimates were similar to those values seen in the other North American H3N2 estimates, especially that Marshfield study. Next slide.

Now I'll transition to the VE estimates performed by our Armed Forces Health Surveillance Division on our active-duty service member component. Next slide. This is also a

case test negative control design. This was done using active component personnel from across all military services, including those stationed in the continental and stationed in foreign locations from, it says September here, but it should say October 2nd through February 4th. These cases are the result of service member outpatient encounters. As in the dependent study, influenza cases were confirmed by PCR or culture. But in this study, we also included rapid test positives for cases. Just a note. And controls were those healthcare encounters testing negative for influenza by either PCR or culture. But negative rapid tests were excluded from identifying those controls. And models In this study were adjusted for sex, age, prior vaccinations, and month of diagnosis. Next slide.

In this, quadrivalent IIV4 was the only vaccine type used in these subjects. It's also important to note that our active-duty service member component population is very highly vaccinated, as influenza vaccination is compulsory for active-duty personnel. An earlier influenza season this year, prior to the typically high 90% vaccination rates in our active-duty, was probably a factor in allowing us to calculate this VE this. But note, nearly every subject here would've been vaccinated against influenza in the prior five years.

And regarding cases, we had a total of 5,560 cases overall with the following case distributions across types and subtypes. Many cases were identified via rapid diagnostic testing in this study, which is why we don't have as many subtypes identified. And lastly, to note, we had too few inpatient cases in these data to calculate VE against hospitalization using a case test negative study design. But I'll touch on that a little bit later. Next slide.

Here you can see our percentage breakdown by age groups for both cases and test negative controls. This population does not contain children or elderly, and 89% of our cases occur in the 18- to 40-year-old age groups. Therefore, as with the dependent VE estimates, these

populations skew younger, and limiting generalization to the broader public, but does focus on that 18- to 40-year-old healthy adult population. Next slide.

Onto our estimates. Here we are showing overall vaccine effectiveness against both Influenza A and B medically attended, laboratory confirmed infections, as well as estimates against A/H1 and A/H3. The adjusted VE for Influenza A in active-duty service members was 35% and was significant. For subtype-specific adjusted VEs, VE against A/H1 was 14% but was not significant, and the estimate had pretty wide confidence intervals there. But for VE against A/H3N2 infection, we observed a 64% estimate that was significant. And lastly, we observed VE against B of 21% that was not significant. Next slide.

So overall, in our active-duty service members, our VE estimates against influenza infections was low at 35% for A and 21% for B, albeit non-significant for B. One limitation here is that we included rapid test positives in our cases, and false positives may influence these estimates. However, of note, due to the nature of the testing, subtype-specific estimates do not include these rapid tests for inclusion. And so the moderately high 64% protection provided by against A/H3N2 infections in this active duty population with the 22-23 Northern Hemisphere vaccine was comparable to our 65% estimate seen in the dependent population and, as mentioned, to those Marshfield studies.

One last note, we did calculate a 54% VE against hospitalized Influenza A using a different studies design, the cohort study design, but it was just shy of statistical significance. And like Dr. Grohskopf, you know, these are early estimates, and we're recalculating as we approached the end of the season. Next slide.

We'll now transition to our phylogenetic analyses conducted by the US Air Force School of Aerospace Medicine. These data just lend a bit more context to those influenza cases,

particularly from the dependent analysis, as these were sequenced data from many of those cases. Next slide. Generally, we'll give a brief overview as you've already had sort of a tour de force from Dr. Wentworth. Next slide.

This figure re-emphasizes the footprint of where our influenza cases originated from this year, with a large representation of around 630 sequences characterized the season from European locations and the United States, with A/H3N2 predominating in these early cases, mostly seen in November and December, and the relative absence of Influenza B in our dataset. Next slide.

For A/H1N1, consistent with what others have seen in North America and Europe and you heard from Dr. Wentworth, we have seen the predominance of the newly designated sub-clades 5a.2a.1 with 76% of our sequences for H1 cases. The 5a.2a sub-clade represented the other 24% of H1 cases. And again, our H1 cases were observed concurrently with H3N2 infections in our populations, making up about 20% of the total cases characterized. But, of note, proportionally here, recently, those cases of H1 represented about 50% of the total cases when we got into January and February. Next slide.

In this tree shown here, the small smidge of red on the, I don't know if I get my little highlighter, but, the red on the side panel on the tree are the current 5a.2 viruses in the 2022-23 Northern Hemisphere vaccines down here. The 5a.2a.1 clade is the large purple portion on the top of the tree. The WHO recommendations for the 23-24 Northern Hemisphere H1 strains include that cell propagated A/Wisconsin/67 virus, which falls at the lone black line on the left-hand side of that panel within that purple clade in the panel just to the right of the tree. The egg propagated recommendation of A/Victoria/4897 falls into the upper portion of this purple clade, showing that threonine-216-alanine substitution, which kind of splits this 5a.2a.1 clade, like Dr.

Wentworth had mentioned. Regardless, consistent with global surveillance partners, the green and blue in the panel on the right of the tree is just to highlight that geographically, these sub-clades were prevalent in both our European and North American data sets. Next slide.

Moving on to H3, we see a similarly high degree of diversity in our data sets as those shown by the CDC, with several competing cade 2 sub-clades fighting it out. The plot here is showing data all the way back to September 2021. So last season when we had a big US Naval Academy outbreak. And sort of showing it back to 2021, you can see the 2a.1a orange, and 2a.3 yellow sub-clades predominated last season in our data set and were replaced by 2b, in pink, 2a.1b, in green, and 2a.1, in the reddish brown. In our DoD ILI cases from this season, making up 93% of the cases and 2b representing the largest proportion of those at 69%, as Dr. Wentworth mentioned.

As a reminder, to all the current and recommended 23-24 compositions of H3N2, they're the sub-clade 2a viruses from the recommendations, as well as what the 22-23 vaccinations were. And we really don't see that specific 2a, and we've seen the sort of maturation of those into the 2a.1b sorry, the 5a.2a.1, and 5a.2a.1a lineages. Next slide. We'll go ahead and glance over that. Oh, I'm sorry. I messed up on the H3N2 sub-clade 2a viruses, which we just really don't see that much of, and they've sort of matured into the 2a.2s, a and b. Sorry. Next slide.

And sort of to highlight that from a phylogenetic perspective, you can see the proportional representation of sub-clade 2b, in pink at the top of the tree, and 2a.1b towards the bottom in green, with several other sub lineages sporadically occurring within those, such as 2a.1 in reddish brown. Also represented, and I won't spend long here, except to mention the panel to the right represents the geographic distribution of cases from September to January. And while the diversity of clade 2b viruses were encountered in both our European and North American

DoD populations, in our European cases, they also showed sort of 2a.1b predominantly. While our North American cases, other than 2b, were also heavily impacted by 2a.1. So again, just to reemphasize that subclade of 3C, 2a.1b.2a.2, the A through D, we mostly saw the As, which were A1B and 1, and then the two Bs also dominating there in pink. Next slide. Next slide, actually.

For Influenza B we have a sparsity of, or sort of scarcity of data here. We only mentioned this because we've only genetically characterized six specimens. And of note, they all fell into the V1A.3a.2 lineages. Next slide.

So, in summary, these data in these data we've shown influenza sequence diversity from primarily North American and European DOD ILI cases. Our data are consistent in that H1N1 cases were primarily from newly designated subclades 5a.2a, and primarily followed by that, of those, the 5a.2a.1 sub-clade. And as a reminder, the vaccine strains from 22-23 were the five A2s, recommended to be updated to these 5a.2a.1s. And for H3N2, we found a broad diversity of competing 3c.2a.1b.2a.2, or a clade two sub-clades. And our cases were primarily 2b, followed by either 2a.1b in Europe and 2a.1 in the States. And B cases were all V1A.3a.2, as I mentioned, and it was unsurprising. Next slide.

Lastly, we'll transition to a quick overview of our antigenic data from these specific isolates that were genotyped. These data are collected by our colleagues at the Naval Medical Research Center in Silver Spring, Maryland. And here we'll be discussing the results from the high content, imaging-based neutralization tests, or the HINT assays, that were discussed earlier by CDC for H3N2, except here we actually run HINT on both H1 and 2 and H3N2. And additionally, our samples were passaged through MDCK cells. And in our analyses, we report the highest elution of ferret antisera generated against various vaccine or candidate viruses. That

showed 50% neutralization of each of our isolates. And thanks to the CDC for providing a lot of those ferret antisera. Next slide.

In this figure, you'll see the traditional antigenic map. Annotated points are representative of what ferret antisera were tested in these data. And those antisera's relative ability to neutralize our former vaccine strains, as well as those in our network. The blue and green samples here to highlight are our DoD isolates. Green isolates here represent older pre-2022-23 isolates, while blue ones are more representative of our current season 5a.2a and 5a.2a.1 isolates. And overall, ferret antisera generated against the recent 22-23 Northern hemisphere, egg and cell, and the recent southern hemisphere 2023 Sydney/5s all have a similar neutralization titer profile, distinct from previous seasons shown here from the green ones on the right. Next slide.

And if we just look at the raw titer table for the same map, you can see the corresponding neutralization titers roughly. Just go off of colors here. The leftmost columns highlighted in bluish gray are the neutralization titers using ferret antisera generated against the 22-23 5a.2 vaccine components. Of note, we do not have ferret antisera against the new 5a.2a.1s. But right next to those bluish gray columns are the ferret antisera against the 2023 southern hemisphere A/Sydneys. Really the main thing to note here are the high antibody titers neutralizing our DoD current season 5a.2a and 5a.2a.1 isolates in the blue rows at the bottom of this table. And we note, however, these are only ferret antisera data, and we do not have the 5a.2 human antisera pools that have been really influential and shown to poorly recognize the currently circulating 2a and 2a.1 viruses. Next slide.

Transitioning to H3N2, again using the HINT assay. You'll see here the annotated samples are representative of ferret antisera neutralization titers raised against recent vaccine candidates. The large portion of blue, yellow, and green points in the middle of this map are

representative of our DoD viruses. Here we do see a slight differentiation of our H3N2 viruses into three distinct profiles or clusters. The reality is that ferret antisera generated against the A/Darwins in the 22-23 and the recommendations for the 23-24, shown on the far left of this plot, did a good job of recognizing and neutralizing the predominant 2as in our study, those being 2a.1b and 2a.1, which are included in the green and yellow clusters shown here. But the blue cluster is entirely comprised of 2b viruses. Next slide.

And to be clear, there was generally good neutralization of these 2b blue cluster viruses, with most neutralizations falling within a fourfold reduction by ferret antisera generated against the Darwin/9 shown in the first gray highlighted column here. However, we did observe many actual eightfold reductions when we looked at the antibody titers for neutralization of the 2b using ferret antisera against cell-propagated Darwin/6, which was a little counterintuitive to what we'd expect based on what Dr. Wentworth had said about cell oftentimes having the different reductions. And so we continue to monitor these, but it still fell within the eightfold reduction. And why not for the sake of time we go ahead and skip the next two. Those are just the other clusters' antigenic table. And here we go.

So in summary, our HINT data for the H1N1 shown here indicate that ferret antisera raised against 5a.2 does well to neutralize circulating 5a.2a and 5a.2a1. However, to reiterate, we don't have human serum pools like those mentioned earlier. For H3N2, our 2a.1b and 2a.1 viruses were well neutralized by either cell or egg-based A/Darwins in the 2a subclade but neutralized 2b less well, specifically for ferret ani raised against cell-based A/Darwin/6. But still within that eightfold reduction for the most part. Next slide.

And so just overall to put our results in context to those recent recommendations from the recent Northern Hemisphere WHO Technical Meeting in February, for H1N1, while our genetic

and antigenic data appear to support the continuance of the 22-23 5a.2 virus strains, our lower VE point estimates for A, overall, in both dependents and service member populations, as well as our poor H1N1 specific VE point estimates for service members does suggest a slightly lower protection by the current 22-23 5a.2 strains. And especially coupled with the human data presented by Dr. Wentworth, we tend to agree with the recommendation to update to the predominantly circulating 5a.2a.1s.

For H3N2, our consistent subtype-specific VE estimates around 65% is really encouraging, especially in light of H3N2, not really having those high numbers typically. These estimates seem to be consistent with other VE estimates that we've seen out of other North American VE networks. And in addition, given the current genetic diversity of clade 3C.2a.1b.2a.2, or the sub clades 2a and 2b predominantly, we've seen here, and the ability of ferret antisera raised against those viruses to neutralize much of the current subclade diversity leads us to agree with that current Northern Hemisphere 23-24 recommendations. And regarding B recommendations, we really can't comment, because we really didn't see it that much and certainly not the B/Yama. Next slide.

And I just want to note that this work is the aggregate result of countless colleagues and public health professionals across the DoD, and I'm honored to have been able to represent those people here. And thank you for your time.

Q & A

Dr. El Sahly: Thank you, Dr. Fries. We have now an opportunity to ask question to Dr. Fries pertaining to the DoD data. Although we're really short on time. But question from Dr. Pergam.

Dr. Pergam: Thanks, Dr. Fries. That was great data to compliment what's been previously discussed. I want to get back to the Influenza B, and I'm sorry I'm kind of stuck on this. But I think you had in, at least in the data for those currently in service, about 200 or so Influenza B cases, but you're only able to sequence 6. Maybe this is just a quick question. Were most of those B-positives from the rapid testing or from PCR? That's, so it was probably potentially false positives potentially. Is that what you guys are estimating from that?

Dr. Fries: That's our working thought at the moment. Yeah. We could only get our hands on so many, and to Dr. Wentworth's point earlier, there is a concerted effort by a lot of our labs going forward to lineage type those, but it does require that extra typing.

Dr. Pergam: Okay. Thank you.

Dr. El Sahly: Dr. Portnoy.

Dr. Portnoy: Yes. Thank you. I'm always pretty much overwhelmed by all of this information, but I do have two questions, two brief ones. Do you, in addition to measuring anybody titers to the influenza vaccines or strains, do you also measure cell mediated immunity? And do you have any information about that? Or does anybody measure cell mediated immunity? And my second question is, do you know what the durability of the VE of the response is? How long does this antibody response last and does it wane over time after the vaccine has been given?

Dr. Fries: Unfortunately, yeah, to both of those questions, those would probably be best answered by Dr. Wentworth in the human serum data. You know, we rely on the ferret antisera data that we see, and we sort of glean from the CDC, so I would have to defer to CDC on that question. Sorry.

Dr. Portnoy: Okay. Thank you.

Dr. El Sahly: Hmm. Okay. We will have an opportunity to ask additional questions during the Q&A. One brief question I have is, given sort of the homogeneity of the population, especially in the active members data, do we see,, in the individuals who have influenza and have been vaccinated, which was 94% of the population, do we see that the strains are any different between those 6% and those 94%? And I ask this question just because you have sort of a controlled environment here.

Dr. Fries: So the first point to emphasize that this year, with the early season, we did not see that high rate. Yes. In the last five years, we can estimate that 94+% have been vaccinated at least once. To your point about some sort of impact of heavy, induced vaccination, those heavy rates, it does create sort of like a natural sieve environment of vaccine sort of pressure. And there are a number of studies being done throughout the DoD and partnership with CDC and NIH on those exact questions of looking at sort of a sieve effect of that. But I'd hesitate to sort of speculate any kind of real heavy impact because of the ability to just drift on a whim sometimes for these viruses, specifically influenza.

Dr. El Sahly: All right. Thank you, Dr. Fries. I see no additional raised hands. To discuss the candidate vaccine strains and potent reagents, Dr. Manju Joshi will be joining us now. She's the Lead Biologist, Division of Biological Standards and Quality, Office of Compliance and Biologics Quality at CBER. Dr. Joshi.

Candidate Vaccine Strains & Potency Reagents — Dr. Joshi

Dr. Joshi: Hope you can hear me. Thank you for the kind introduction. As she mentioned, I am the Lead Biologist in the Laboratory of Biochemistry, Virology, and Immunochemistry in the Division of Biological Standards and Quality Control, in Office of Compliance and Biological

Quality at CBER. In today's talk, I'm going to just give you an idea about the candidate vaccine strains and the potency reagents, very important ones, which are needed for vaccine testing. Next slide, please.

So mainly, I'll just cover two aspects. One will be what are the WHO recommendation for 23-24 northern hemisphere influenza vaccines. And I will give you an idea about the availability of the potency testing reagents for each of the recommended strains. Next slide please.

So, WHO recommended viruses for Influenza A, H1N1 type for 23-24 Northern Hemisphere vaccine season is different from the 22-23 Northern Hemisphere season, and is also different from what was recommended for 2023 Southern Hemisphere season. For egg-based vaccine, WHO recommended that A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-derived vaccines. While for cell culture or recombinant based vaccine, WHO recommendation is for A/Wisconsin/67/2022 (H1N1)pdm09-like virus, which is MDCK cell derived. Next slide please.

So as far as the availability of the candidate vaccine viruses are there, this was from the most recent list from the WHO website, and I'm sure more viruses will be added to the list in the due course as the candidate vaccine viruses become available. But for A/Victoria/4897 wild viruses as well as candidate, CVV, which is IVR-238, has been made available by VIDRL in Australia. Next slide please.

For A(H1N1)pdm09 CVVs, for cell culture-based vaccine, two viruses have been recommended, which are available on the WHO website currently. And one is the A/West Virginia/30/2022. And the second one is A/Georgia/12/2022, which are available from CDC in US. Next slide please.

So we have to always think about the potency reagents. In the event this committee approves or goes with the recommendation made by WHO, potentially testing reagent will be required for this new strain. As always, CBER will work with essential regulatory ERLs, essential regulatory laboratories, the ERLs, and with manufacturers to prepare and calibrate the required reference antigen for testing of the vaccines produced in egg platform and cell culture, and for recombinant vaccine, as well. And since the serum production takes some time, we are already planning into the process of making antiserum for this train, provided Committee approval of this train. Coming to the next slide. Next please.

So as for Influenza A of H3N2 type is concerned, WHO recommended virus for 23-24 Northern Hemisphere season vaccine is same as for that recommended for 22-23 Northern hemisphere season. And it's also same as the this which was recommended for 2023 Southern Hemispheres season for egg-based vaccine. WHO recommends that A/Darwin/9/2021(H3N2)-like virus be used in the vaccine. And WHO recommendation for cell culture- or recombinant-based vaccine is an A/Darwin/6/2021(H3N2)-like virus. So since these strains have been used for past two seasons, candidate vaccine virus is, many of them are available and have been successfully used in past vaccine production campaigns, and they are all the state on WHO website. Next slide please.

So if, again, every time I had to reiterate that if Committee approves of this strain to be included in the vaccine for US campaigns, I'd like to give you an idea about the potency testing reagents, which are available for testing of vaccines. As always, we work in collaboration with essential regulatory laboratories all over to ensure that reagents are available for testing. Here in the table, I have listed all the reagents which are required for testing of vaccines made in different platforms. Just want to highlight what we have available in our stocks is for the

A/Darwin/9 cell-based, reagents for A/Darwin/9 SAN-010 CVV. At the same time, we have the reagents, both reference antigen as well as antiserum, available for A/Darwin/11/2021 cell platform, as well as A/Darwin/6/2021 for the recombinant platform. Additional reagents are also available for various different assortments or viruses from our ERL partners as well. Next slide please.

Coming to the Influenza B for the from the Victoria Lineage, WHO recommended virus for 23-24 Northern Hemisphere season for both trivalent and quadrivalent vaccine is same as the one for 22-23 Northern Hemisphere and what was for 2023 Southern Hemisphere season. WHO recommends that for egg-based vaccine, B/Austria/1359417/2021-like virus be used. For cell culture or recombinant vaccine, it's the same virus. Same virus, which is MDCK cell derived. Again, candidate vaccine viruses, many are available. And as for H3N2, these have been used in past vaccine production campaigns. Next slide, please.

Just to give an idea about that, if this strain was included and how are we going to be dealing with and what are the reagents available for these strains? Again, I would like to point out that for past campaigns we have produced reagents for the egg platform. In the interest of time, I'm not going to read all the details of it, but here's B/Michigan/01/2021, which is a B/Austria-like antigen and was used in vaccine. CBER had provided reagents for testing of those vaccines. At the same time, we had prepared reference antigen reagents for B/Singapore/WUH4618/2021, which is a B/Austria-like antigen and was used in cell platforms, and as well as for B Austria reference antigen, that strain, which was used in recombinant platform. So all these three agents are available from CBER currently. There are other reagents as well, available as well, which are listed on the table from our ERL partners as well. Next slide please.

So coming to the second B strain, which is from B/Yamagata Lineage, WHO recommended virus. For 2023-24 Northern Hemisphere season is same as the one which was for Northern Hemisphere campaign last year, and as well as for the ongoing Southern Hemisphere season. And as all of us, we know that this has been a part of vaccine for several, many years. So it's a B/Phuket/3073/2013-like virus for egg vaccine. And same is true for the recommendation for cell and recombinant vaccine. Next, please.

Again, I've listed here, if Committee approves of this inclusion in the vaccine, the reagents that will be needed for the testing of vaccines are available as listed up here. Reagents for egg platform testing, as well as for cell and recombinant platforms, are available from CBER, as well as from other essential regulatory laboratories as well. So next slide, please.

So I would just like to conclude in saying that I've provided you the situation about the vaccine testing reagents if the WHO recommended strengths are approved by today's committee and are included in vaccine. Just, not so much for committee, but for the general audience who are listening to this meeting, I just wanted to say is they can, as far as CBER reference standards and reagent ability and shipping is concerned, they can contact us at this email address I have provided here. And if you have any questions regarding, or you have any feedbacks or comments or any general inquiries regarding reagents or testing of the influenza vaccine, we have our CBER influenza feedback mailbox, and the email address is provided here. So we can be contacted, and we will be happy to help it out. So we are going to direct all our efforts to make sure that all the reagents are available in timely manner and the vaccine testing and release goes on, for the public, the vaccine testing goes on in a smooth manner. Thank you. And I can take any questions.

Dr. El Sahly: Hmm. Thank you, Dr. Joshi. Any of the committee members with questions for Dr. Joshi, please use the raise your hand function. I do not see any raised hands. Thank you, Dr. Joshi.

Dr. Joshi: Thank you.

Dr. El Sahly: To provide comments from manufacturer representatives, we have Dr. Elizabeth Neumeier, Director of the Technical Lifecycle Management, Influenza Global Vaccine Manufacturing, science and Technology at GSK. Dr. Neumeier.

Comments from Manufacturer Representative — Dr. Neumeier

Dr. Neumeier: Yes. Thank you very much. Thank you, Dr. El Sahly. I'm having trouble to start my video. I apologize for that. So I would first like to thank the VRBPAC committee and the FDA for the opportunity to share the industry perspective on influenza vaccine manufacturing. I am making this presentation on behalf of all manufacturers who supply influenza vaccine to the US market. Specifically, these are Sanofi, AstraZeneca, Seqirus, and GSK. Each of these manufacturers has contributed to this presentation. Next slide, please.

So here is my disclosure statement. I am an employee of GlaxoSmithKline, and I own shares in the company. Next slide, please.

So to summarize some of the key messages and to give an overview of my presentation, I will give an overview of our vaccine production, release and distribution timelines, the preparations that we make together with the public health service organizations throughout the year, and some insight into some of the challenges that we face as vaccine manufacturers. Next slide please.

So, a successful influenza vaccination campaign is a team effort. The goal is clearly to provide an influenza vaccine that is well-matched to the circulating influenza viruses in sufficient quantities and well before the start of the influenza season, so that everybody for whom vaccination is recommended can be protected in time. If we start from the top and move around clockwise, the first key success factor is to have a vaccine that is well-matched to circulating strains. And we heard some allusions to that already today, that the H3 virus seem to be a good match. And this is visible in the good protection. This selection of well-matched strains is based on ongoing and robust surveillance of circulating influenza viruses. And this data provides the WHO and this committee with the required information to make that decision.

The next circle shows that the time needed to select the best strain must be balanced with the time that is needed by manufacturers to produce and distribute the vaccine before the start of the influenza season. So here, it is critical that strain selection and supply of candidate vaccine viruses and potency reagents is in time for manufacturers to evaluate the available CVVs, and to select the ones that work best in our respective manufacturing processes so that sufficient quantities can be produced. All these elements play together to produce a well-matched vaccine that is available before the start of the influenza season in sufficient quantities to protect all those who need it. Next slide please.

This slide gives an overview of the influenza detections reported to FluNet in the United States since 2019, meaning before the start of the COVID-19 pandemic. The pattern clearly shows the impact that the COVID-19 pandemic had on flu circulation after the onset in 2019-20. There were very few cases during the 2020-2021 season. However, there were isolated pockets of influenza activit,y and antigenic drift continued so that antigenically distinct variants evolved

even though influenza circulation was very low. Influenza activity resumed, then, late in the 2021-22 influenza season, but went on far into the first half of 2022 in an unusual biphasic curve.

Now in this influenza season, the 22-23 season, we saw an early onset of influenza circulation with a very high peak that for the influenza detections exceeded the pre-Covid level but dropped off early rapidly in January. And we heard all about it from Dr. Grohskopf and Dr. Wentworth. Influenza circulation appears not to have returned to the pattern that we were used to seeing before COVID-19, but although circulation has been low and irregular in some seasons, the evolution has continued and required updates to the vaccine composition. Next slide, please.

So if we look back at the Northern Hemisphere 22-23 season, there were two strain changes recommended by the WHO and confirmed by this committee. Both components had already been a component of the preceding 2022 Southern Hemisphere vaccine. That means that candidate vaccine viruses and potency reagents for the new strains were readily available at the time of the vaccine recommendation. And their availability was not a limiting factor in the production campaign. So the 2021-22 season was not one of the more challenging ones, because virus and reagents were available early. And also an important factor, the new viruses had acceptable yield in the manufacturing processes. Next slide please.

This slide gives a snapshot of the main activities that occur each season that have to be done to achieve the US supply timeline. Many of you may recognize this slide. We have used it in in previous years already. So in order to meet the vaccine demand, manufacturers begin to produce at least one of the three or four vaccine components at risk before the vaccine strain selection meetings. And to mitigate that risk, we use surveillance data that is available at the time. This is shown in the yellow bar. And just a general comment, the slide is broken down into

the upper panel, which shows the activities that go on in public health sector, and the lower part of the graph shows the activities that are part of influenza vaccine manufacturing.

So once the annual strain selection meeting occurs, and it is shown as the blue triangle on top of the graph, once that meeting occurs, production of all vaccine component begins. And of course, if there is a strain change, we have to start with producing new working virus seeds. And in parallel, potency assay reagents are produced by our public health partners. So since we can only produce, or since we start to produce these working seed viruses once the vaccine composition is confirmed, this already emphasizes how important it is to have these viruses available early.

Production continues, then, with all four components. Not all four components may have the same yield, so different amounts of batches may be needed. Towards the end of the campaign, balancing of manufacturing is done to ensure that we have equal amounts of each vaccine component produced. And the antigen yield of the least productive vaccine strain is actually the rate limiting factor and determines the number of vaccine doses that are supplied and also the supply timelines.

In order to formulate the vaccine, which is shown by the blue triangle just between May and June and the arrow that is pointing down from the public to the manufacturing section. So in order to start blending the vaccine components, we need potency reagents, and we start immediately once those are available. But of course, we need to wait until these are available from the health authorities. So again, a very critical time point in the manufacturing campaign. When, after secondary manufacturing has started formulation, filling, packaging, and distribution can start. And this process extends into the fall, when vaccination is recommended.

You can see from the slide that it takes about six months to manufacture, release, and start distribution of the volumes of vaccine doses that are required for the season. The timelines are very compressed. In a period of eight months, we have to supply, so all manufacturers have to supply a total of up to 200 million doses to the US market. And most manufacturers also supply other countries. And the total volume that is produced and distributed globally is more than 500 million doses. Early demand planning is very critical to ensure sufficient supply of vaccine, because once the campaign is planned and ongoing, it is next to impossible to produce more volumes than have been planned well before the season. If any of the components in these timelines start to slip, it will impact vaccine delivery for the annual vaccination campaign and will delay the volumes that are available to the patients.

So, in summary, influenza vaccine manufacturing is determined by the need to distribute and administer vaccine well before the season peak, the availability of the candidate viruses, and critical potency reagents for the vaccine suppliers. Next slide please.

The seasonal influenza vaccine supply requires a well-coordinated timing among a number of key players. And some time ago, we came up with this analogy of a relay race, where members of the team take turns performing their roles. So the race starts with the strain selection process by WHO collaborating centers, the essential regulatory laboratories, and the high yield reassorting laboratories, who then hand off the baton to the manufacturers. At the time of the strain selection, manufacturers, as I said, have already started to produce vaccine at risk, and we are at full speed when the handoff occurs of the new strains and the new formulation.

There are some special challenging for influenza production in this relay race, and this includes multiple candidate vaccine viruses, production of multiple reagents, and also multiple vaccine types. Multiple providers, such as WHO collaborating centers, essential regulatory

laboratories, and high yield reassorting laboratories. For each season, we are also facing hurdles that can be specific for that season. For example, in the 2022-23 season, we had two strain changes for H1N1 and H3N2. However, as I said, CVVs and reagents were readily available, so there were no delays due to the availability of these critical components. The Nagoya protocol, which I will discuss in some more detail in a couple of slides, can also impact timely availability of the best matched vaccine virus or DNA sequence. In the 22-23 season, the CVVs were not impacted by the Nagoya protocol.

For the 2023-24 season, if we take an outlook, the WHO recommended to change the H1N1 component. If this committee follows the WHO recommendation, new CVVs and reagents will be needed for the H1N1 vaccine component. And Dr. Joshi, just before my talk ,already laid out some of the details for this process. For the currently available CVVs for the new H1N1 component, we also do not expect issues coming from the Nagoya protocol.

I think this is a good time point to take the opportunity to really thank our collaborators in the public health sector and to acknowledge the successful collaboration we had over many years, which enables manufacturers to provide the required number of doses at the time when they're needed. So thank you very much on behalf of all the manufacturers that supply the US markets. Next slide please.

So here I'm showing the cumulative number of doses distributed in the United States over the last three influenza seasons. We can see at the first data point that a relatively high volume was available early in the season. And if we move on through the timeline, most of the required doses have been largely distributed by November. To date, in the current season, approximately 175 million doses have been distributed. This is comparable to the 2021-22 season, but it falls

short of the flu season of 2020-21. On the next slide, this is even more visible. If we can move to the next slide, please. Thank you.

So here we see two graphs that show the accumulated number of doses distributed to the US market over time. And if we start with the bottom right graph, it shows the evolution of the vaccine demand over the last 40 years. So there has been a steady increase and an overall rise in the total doses over time. However, it also shows what I just said, the drop after the 2020-21 season, and you will notice that the graph stops with the 21-22 season. So we expect either the same level or potentially even lower for the current season.

Apparently, the influenza vaccination uptake has also been slower and lower than in previous seasons, and I cannot speculate what the reasons are for that. But it is critical to understand that the supply of vaccine doses is driven by demand, and it is very critical to emphasize the importance of vaccination for all groups for which vaccination is recommended. I mentioned it earlier that planning of production volumes occurs well before the influenza season and higher volumes cannot be produced at short notice. For example, if a severe influenza season is expected. Next slide please.

So to summarize our review of the 22-23 season, we had a very high influenza peak early in the season. Influenza vaccine was available early. The vaccine demand was lower compared to previous years. And as we also heard the good news that in this season the VE flu vaccine provided substantial protection, which is what we are all working towards. Next slide please.

So I'm now switching gears and I will present a few slides on the Nagoya protocol and the impact of the Nagoya protocol on seasonal influenza. Just to provide a little bit of background, the Nagoya protocol on access and benefit sharing is an international treaty supplementary to the Convention on Biological Diversity, CBD, which was adopted in 2010,

with the objective of fair and equitable sharing of benefits arising from the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity. An increasing number of countries have enacted Nagoya protocol and/or national ABS, so access and benefits sharing legislation. And in many cases, genetic sequence data are now included within scope. Next slide, please.

For the influenza surveillance in the Influenza Surveillance Network, most national influenza centers continue to supply influenza viruses under the agreed terms of reference as part of the Global Influenza Surveillance and Response System, GISRS. However, there is often a lack of legal clarity if the viruses can be used for vaccine manufacturing and research. If we look at the two world maps and compare the locations of the National Influenza Centers in the WHO GISRS and the countries that are party to the Nagoya protocol, that's the map on the right hand, it is very clear that there are already significant overlaps. And as more countries become party to the Nagoya protocol, this may have an impact on increasing number of national influenza centers that supply viruses to the WHO network. Next slide, please.

If we take a step back and look at the more global impact of the Nagoya protocol, it is important to realize that the sharing of pathogens and their associated information must be fast, easy, and legally certain. In recent years, national Nagoya and other access and benefits sharing legislation requiring bilateral negotiations has created significant bureaucratic hurdles which make it increasingly difficult to achieve. There are already more than 100 distinct ABS laws around the world, which potentially impose legal requirements for benefit sharing that companies must navigate in return for access to pathogens.

Although the Nagoya protocol recognizes the importance of public health, only 12 countries out of 137 have ABS rules that include a public health emergency provision, which is

critical for rapid and unimpeded sharing of pathogens. This has weakened legal certainty in access to pathogen samples and sequences, with negative consequences seen already in the sharing of a number of viruses, including seasonal influenza. In the case of influenza viruses, since 2018, vaccine manufacturers have seen delays ranging from three weeks to nine months before being able to access around 40 important influenza samples. And if you remember the timelines I have shown previously, a delay of nine months makes a virus unusable for a given influenza season. Next slide please.

So, the timely sharing of pathogen samples and information is critical and essential for responding to potential epidemics and pandemics. The inclusion of pathogens, including influenza under national ABS legislation continues to cause delays and disruptions. Approximately 40 influenza viruses have already been impacted by national Nagoya protocol or ABS legislation, incurring significant delays before legal clarity could be obtained. And the legal certainty regarding the number of the status of pathogens sharing is essential in the context of vaccine manufacturing. Next slide, please.

So, I'm including, or we manufacturers are including, one slide on the circulation of avian influenza viruses in wild birds and poultry. This is a topic that has very high attention at the moment because, since October 2021, an increasing number of outbreaks of avian influenza has been reported in wild birds and poultry worldwide, with expanding geographic regions being impacted. Another important point is that infections of mammalian species have been reported with high frequency. Despite all that, the risk of human health is currently still considered to be low. And of course, this is continuously monitored carefully. If new antigen variants emerge, new CVVs that match these variants are prepared by the WHO network and are made available to industry. The response to a potential pandemic threat requires coordination among all

stakeholders in the public and private sector, and a continuous dialogue to guide the efforts of industry so that we reach the best possible level of preparedness. Next slide please.

So to summarize, two components of the 2022-23 influenza vaccine were updated to match circulating viruses, CVVs, and potency assay reagents were available early. To date, approximately 173 million influenza vaccine doses were supplied to the US market. However, it has to be noted that vaccine demand was lower compared to previous years. Influenza vaccine provided substantial protection this season. The Nagoya protocol and ABS legislation is posing an increasing challenge and impacts the ability to select and manufacture the best vaccine strains. Confidence in influenza vaccination continues to be of great importance as flu circulation returns to pre-COVID-19 levels. Next slide, please. So I would like to thank you for your attention, and I'm happy to answer any questions.

Q & A

Dr. El Sahly: Thank you, Dr. Neumeier. Please use it, the raise your hand function to ask questions to Dr. Neumeier. Okay. So I have a clarifying question. The flu distribution, it's also the uptake, right? Not just what went into the market, it's what went into the arms?

Dr. Neumeier: My understanding is it's the doses distributed to the market, not necessarily what has been used to vaccinate.

Dr. El Sahly: Okay. Okay. So to that, I may have a question then to Dr. Grohskopf. Did we see that trend you know, the distribution going year by year, also the uptick? Has it been going year by year in the last two, three years?

Dr. Grohskopf: You mean, sorry, Dr. El Sahly, has it been increasing, has the, has coverage been increasing or changing the last two, three years?

Dr. El Sahly: Yes. The distribution has been decreasing according to Dr. Neumeier's data. But that is distribution. Has the uptake also been decreasing, or is it more steady in our country?

Dr. Grohskopf: It depends on the group that you're talking about. There have been drops in coverage over the last two seasons, particularly in some groups. And they're more in some racial and ethnicity groups than others. Coverage among pregnant women has been a bit lower the last two years. So there has been some concern about drop in coverage.

Dr. El Sahly: What about individuals older than 50 or 60? Are we still, they used to have the best coverage. Are they still good there?

Dr. Grohskopf: In general, theirs tends to be more stable.

Dr. El Sahly: Thank you. And then I have a question about the Nagoya protocol. I know we hear about it every year, but I wonder if it has more of an impact on avian pandemic influenza than seasonal influenza. I guess in my, I guess simplistic interpretation of what I see, that may be the case. But what are your thoughts on that?

Dr. Neumeier: The impact is primarily on seasonal influenza vaccine manufacturing and strains. At the moment, for pandemic viruses, they are also in scope. However, we do have a framework already for the availability and distribution of zoonotic influenza viruses, the PIP framework. It is still under discussion whether there's also obligations for pandemic viruses under the Nagoya protocol or whether that is covered by the PIP framework.

Dr. El Sahly: Okay. Alright. Thank you. Couple of questions. First, Dr. Perlman.

Dr. Perlman: Yeah, I just had two almost technical questions. So the first, with the problem about getting some of the viruses shared, do the manufacturers have the ability to use recombinant technology to just make the viruses instead of having to get them shared? Or is there something more to sharing than that?

Dr. Neumeier: To a degree, that depends on the license of the manufacturers. At the moment, I'm not aware that any manufacturer uses recombinant viruses, so genetically engineered viruses. And even if that were the case, the sequence information is also covered by the Nagoya protocol. So even recombinant viruses would fall under the Nagoya protocol potentially. That depends a little bit on the national legislation in the respective countries.

Dr. Perlman: And does the last statement that you made mean that if one manufacturer has a virus, that the manufacturer cannot share it with other manufacturers, or how does that work?

Dr. Neumeier: Generally speaking, all reassortments that are prepared for seasonal influenza vaccine are available to all manufacturers. It is true that genetically engineered viruses have intellectual property, so fall under intellectual property rules. That would create a precedent and would have to be discussed and agreed with the license holders, the use of such viruses. In some countries, for example, in the EU, recombinant viruses also fall under, would require a different licensing procedure than the procedure that the current seasonal influenza vaccines are licensed under.

Dr. Perlman: Thank you.

Dr. El Sahly: Dr. Monto.

Dr. Monto: Just to comment. You beat me to it, in terms of the Nagoya protocol, it's something that comes up periodically, is viewed in some ways as the potential showstopper in terms of getting vaccines, including pandemic vaccines. I remember the first time I heard about it was about getting H5 viruses out of Indonesia some time ago. And if it truly is a problem, then it would be appropriate that we do this. Not in the context of just flu, but in the context of vaccines. Vaccines in general. Just an overall comment.

Dr. El Sahly: Thank you, Dr. Monto. Dr. Janes.

Dr. Janes: Thank you. Another point for clarification. I believe that the Nagoya protocol, as discussed, only impacts, or should only potentially impact manufacturer vaccines. But I just wanted to clarify, is there any concern or potential for the Nagoya protocol to impact sharing and characterization of viruses that are circulating the population, and thereby characterization of circulating sequences and immunogenicity associated with vaccines against those sequences?

Dr. Neumeier: Perhaps Dr. Wentworth would be best to answer that question.

Dr. El Sahly: Yes, hand raised. Dr. Wentworth.

Dr. Wentworth: Thanks, Elizabeth. And yeah, so there really is very little impact on the sharing of the reagents for characterization and surveillance, because all of the NICKS, their terms of reference, really involve sharing. And we're really working, the WHO Global Influenza program is also really working with the National Influenza Centers to even update their terms of reference, so they have a better understanding of the Nagoya protocol. If a virus of theirs were to be selected to be a manufactured as a vaccine, so that we could potentially alleviate some of the process. I mean, just because you're a signatory doesn't mean it couldn't end up as a vaccine, but they have to give permission, the right authority within that country has to give permission to use it as a vaccine, free and clear to the manufacturers. And so that's where the uncertainty, and it causes a lot of uncertainty. And I really do understand what the manufacturers are saying, but I really want to distinguish those two things. That's why I raised my hand. Because when it comes to the sharing of viruses, it has very, very little impact on that. It's more in the vaccine development phase.

Dr. El Sahly: That's reassuring. Thank you, Dr. Wentworth. I do not see raised hands. Any final questions to Dr. Neumeier before break? Okay. Hearing none. And I'm going to get the time right this time. We have to start at 1:30 on the dot, because that's the Open Public Hearing, and it

has a specified time we have to follow. So at 1:30 PM Eastern Time, we reconvene for the OPH session. Thank you all.

Open Public Hearing

Dr. El Sahly: Good afternoon, everyone. Thank you all for joining in the afternoon. Next on our agenda is the Open Public Hearing session. I will be going over the Open Public Hearing announcement for Particular Matters Involving Specific Parties. Welcome to the Open Public Hearing session. Please note that both the FDA 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 or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, it's 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'll not preclude you from speaking. I turn the meeting now to Dr. Sussan Paydar. Dr. Paydar.

Dr. Paydar: It goes to Ms. Valerie Vashio today. She's my alternate DFO.

Dr. El Sahly: Okay, Ms. Vashio.

Ms. Vashio: Thank you, Dr. El Sahly. Before I begin calling the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in

its decision-making processes. Every advisory committee meeting includes an Open Public Hearing, OPH, session, during which interested persons may present relevant information or views. 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 with our one OPH speaker who pre-registered for speaking today. You will only have four minutes to make your remarks. Sarah Barry.

Sarah Barry — SAFE Communities Coalition

Ms. Barry: Hello. Am I okay to start speaking now, I assume?

Ms. Vashio: Yes, Sarah.

Ms. Barry: Okay. Thank you very much. Yes. My name is Sarah Berry. I'm the Volunteer Director of Research and Media Relations for SAFE Communities Coalition, and I have no known conflicts. Next.

Dear committee, thank you for allowing me to speak today. I want to note that I am the Volunteer Director of Research and Media Relations for SAFE, and I think that that's important context for later in this presentation. Next.

SAFE Communities Coalition is still a relatively new organization that was started by grassroots vaccine advocates who, like myself, saw the influence of anti-vaccine and anti-science rhetoric taking over. As a non-partisan organization, we support any common sense public health legislation and candidates who will fight to pass it. Next.

I had previously given a presentation to this committee regarding anti-vaccine lobbying, and today is simply an update to that information. Next. Anti-vaxxers represent a cultural force that goes beyond questions about vaccines. As we shared last time, there are numerous anti-vaccine 501c3s, c4s, LLCs, and PACs that work often in tandem with one another to accomplish an overall anti-public health agenda. Next. However, these groups are also the source and funding behind numerous petty lawsuits, and that's a trend we've seen growing. As the director of research for SAFE, I see firsthand how many active lawsuits are a direct result of anti-vaccine efforts. Next.

These lawsuits, again, the anti-vaxxers themselves, are quite candid about the origin and purpose of these lawsuits. And these lawsuits often target public health employees and agencies and their employees. And regardless of whether a lawsuit is successful, the mental strain and financial burden is real. Those are resources and time that could be spent on other more legitimate efforts. The most alarming example I have found of this involves an attorney general who is working directly with local anti-vaxxers and openly displayed anti-vaccine propaganda while deposing Dr. Fauci. Next.

Now, I know that sounded kind of scary, but the good news is that SAFE is working in partnership with other grassroots groups such as Louisiana Families for Vaccines. Louisiana Families pushed back against the rising tide of anti-vaccine legislation in their state by showing up with friendly faces and important information. And because of their efforts, all of the anti-vaccine legislation in Louisiana was successfully killed in 2022. We're obviously hoping for a repeat of that in 2023. Next.

The bad news is that anti-vaccine extremism is growing, and we've seen with that a rise in the total number of vaccine related legislation introduced all over the United States. Montana

is in particularly bad shape, as they are currently debating a bill that would prohibit Covid vaccinated persons from donating blood, and they are the first state poised to expand non-medical exemptions to routine school immunizations in over 20 years. I can confirm that not only are the anti-vaccine groups working hard to get these bills in Montana passed, but they're also doing so with direct assistance of the legislators in that state. Next.

Without naming names, I think it's important to put into perspective how much the largest anti-vaccine organization is spending on their efforts to roll back public health. Next. After going through publicly available job listings, I estimate that the largest anti-vaccine organization is at an absolute minimum spending 1.3 million a year just on payroll. All of these job listings offered insurance and 401k, but without knowing the quality of those benefits, I simply excluded them from this estimate. If we were to include benefits, travel events, and the copious amounts of money they are spending on lawyers, my best guess for their yearly operating budget is no less than 10 million. Next.

Yes, one anti-vaccine organization, just one, is almost certainly spending at minimum 10 million a year. And that might seem like a scary number. And truth be told, I hope it scares you just a little bit. Some of you are probably wondering how they can afford such a large budget, and I can confidently tell you it's because this same organization, by my estimate, has raked in well over 20 million dollars in the past few years. And some of those pieces of information, it's hard to quantify that because certain financial documents and 990s have not become public knowledge yet. But I imagine that our understanding of exactly what this anti-vaccine ecosystem looks like will change as more this information comes out. Next.

So, SAFE Communities Coalition is a team of three and one volunteer, and that is me. And as I said, I do not get paid. I have no conflicts of interest. I am a volunteer. I do this out of

my own time and passion for this issue and for how much I care about it. And I see how much more resources the anti-vaxxers have versus all vaccine advocates. And I'm not just talking about SAFE Communities Coalition. I do not think, but this is just, the estimates I gave you were from one organization. If we were to take the totality of all of the anti-vaccine organizations that are working together, I mean, that number, I don't, we didn't even know where to start. So I just want to emphasize the importance of promoting vaccine, pro-vaccine legislation, promoting pro-science candidates. And obviously SAFE Communities Coalition is here as a resource for anybody, whether it's the people on this call or anybody listening now in the future. You know, please reach out to SAFE Communities Coalition. We have excellent information. I can attest to that from firsthand knowledge, excellent information on the anti-vaccine movement and where the pro-vaccine movement is going as far as legislation and lobbying. So I really thank you all for your time. And if you have any questions, please email them to us at info@safecommunitiescoalition.org. Thank you very much.

Ms. Vashio: Thank you, Sarah, for your comments today in your presentation. We appreciate it. This concludes the Open Public Hearing session for today, and now I hand over the meeting back to our chair, Dr. El Sahly. Could you please start the next session?

Dr. El Sahly: Thank you, Ms. Vashio. So, during the next portion of our meeting, for which we have dedicated one hour, we will be discussing the four questions that we will be voting on. Dr. Paydar, should we display them or just begin the discussions first?

Dr. Paydar: We need to display the four questions and discuss them.

Dr. El Sahly: Alright, let's display. Okay, so here are the four questions to be discussed today. I'm going to go over them. First question one. For the influenza A (H1N1) component of the 2023-2024 influenza virus vaccines I the U.S., does the committee recommend an

A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2019 (H1N1)pdm09-like virus for cell- or recombinant-based vaccines? And that is a change.

For the Influenza A H3N2 component of the 2023-2024 influenza virus vaccine in the US, does the committee recommend an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- or recombinant-based vaccines? And that is a change.

For the influenza B component of the 2023-2024 trivalent and quadrivalent influenza virus vaccines in the U.S., does the committee recommend inclusion of a B/Austria/1359417/2021-like virus of the B/Victoria lineage?

For quadrivalent 2023-2024 influenza vaccines in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus of the B/Yamagata lineage as the second Influenza B strain in the vaccine.

So I invite our committee members to use the raise your hand function so I can see who has a question. And I think all of our presenters from this morning and the FDA are present to help answer questions or listen to our comments. I see the first hand by Dr. Gans.

Committee Discussion, Recommendations, and Vote

Dr. Gans: Thank you so much, Hana. I'm going to leave my camera off if that's okay. I really appreciated all of the really in-depth presentations that we had this morning and usually have during this meeting. And really gets us to be able to review the data that actually would obviously contribute to these questions. So I am in support of the recommendations that come forth from the thorough work that the WHO and CDC and our other colleagues put forth. I do

want, just because we seem to always be in the same situation, these are highly effective mechanisms for helping public health, obviously, and vaccination is the way to go. And we have these vaccines that are helpful in really contributing to the particularly severe outcomes, as we've heard.

I just want to put in the record some of the things that have been discussed previously, but apparently, we need to get them into the public record that we really do need to move the conversation forward. And that includes from the epi side more subtype testing, and a lot of that was already raised, that that is being done. But we really need to be able to understand the strains and clades that are moving this forward and how we choose these. We need more nuanced information in terms of what, how to break down some of the epi data, not just taking a hammer to it. And that includes different populations who may be at more risk and more value of these vaccines and some of the more nuanced outcomes in terms of ICU and mortality. We also need information, as been raised, that influenza doesn't circulate alone. And what are some of the coviral infections or other co-infections.

We also, obviously from the immunology standpoint, which we've been talking about for a long time, even though we call the humoral immunity, these correlates of infection, we need more nuanced information about immunology and T-cells. We've been asking for a very long time. And we also need the studies that would allow us to move the components of the vaccine forward, as we've discussed with the H3N2. It seems that our inability to get that information maybe has allowed the H3N2, which now we see as predominating. We really maybe allowed that to happen because we've done such a good job with the other ones. And obviously there's other environmental stressors that are going, or impacts, that are going along with that.

And lastly, I think what I would love to see, and I'm sure other people on the committee, but I won't speak for them, is to really bring forward also the continued and great work that's being done looking at the safety of these vaccines, which we know are incredibly safe. And it would be lovely to have those, that data that we know is collected globally, as well, really come forward and discussed when we're looking at these vaccines so that we could look at all the data together. So I appreciate the work that has been done. I appreciate the conversations that we've been having to move this discussion forward, and I just wanted to put that into record.

Dr. El Sahly: Thank you, Dr. Gans for the summary and the comments. I have a question from the morning to Dr. Wentworth. It's more of a clarification regarding the process. So what we saw that, for the H1N1, the ferret sera, there wasn't much of a distinction between the Victoria of last year. Is it Victoria? Yes, the Victoria of last year and the currently circulating strains. However, when we used human sera, we did detect a divergence in the antigenicity between the vaccine that was used last year and the circulating strains. And I think, as I understand it, it has to do with the recognition of the epitope, kind of in the northeast of the HA, as you displayed it for us.

But what if the reverse is true? Let's say the ferret data would show diversions, significant diversions between the strain used previously in the vaccine and what's beginning to circulate. Yet the human data don't show that divergence by virtue of recognizing other epitopes. Would, what, how would that have changed recommendations? Or would it?

Dr. Wentworth: Yeah, that's an interesting hypothetical question.

Dr. El Sahly: Oh, so it doesn't happen ?

Dr. Wentworth: Yeah. Yeah. Well, I mean, it is, it doesn't really happen. So the ferret is a model, an animal model, and it, like all animal models, is imperfect. And what we've grown to understand is with the H1N1 pdm09 viruses in particular, it tends to be quite immunodominant to

that site SA side of life and not as immunodominant to the SB side. So you were dead on in your question. So now let's imagine that that inverse happen. We're seeing distinction in the ferret, but we're not seeing it in humans. So there'd be the triangulation of multiple types of data. So you have the genetic data of all the viruses that are circulating, and the evolution that you're seeing there, which is kind of a reflection of generally immune escape. I mean, that's the biggest fitness driver in humans for influenza drive, influenza viruses, is immune escape. And so sometimes you might see parallel evolution that's happening that's in agreement with the ferret data or in disagreement with the ferret data. So you would have, you would have that aspect of it.

Then we would take the human era and we would break it down. Right? So if you were to look at the 6 month to 36 month old age group in humans, and you're not seeing something that the ferrets are seeing, that would suggest that the ferret model is actually incorrect in that scenario. And to top it off, if you had VE that was consistent with H1 VE, and you had those viruses cocirculating at the time. So that's a, there's a couple of ifs there. Sometimes you don't have enough of the variant that's cocirculating for VE to be an estimate. But if VE wasn't changing, then you would believe the human side of the equation.

But if the opposite was true, we're seeing it in naive kids. There is evolution happening. That's really, really looking like this is a fitness advantage. And we use a lot of different tools there in the genetic space, local branching index. So how many changes are happening in that site. Known epitopes and crystallography with human monoclonal antibodies, understanding that they're in known epitopes is very important. That's why I show the molecular structures and point out certain amino acids. And so it would really be, it's never just one piece of data. It's the triangulation of multiple pieces of data.

And then, finally, kind of getting to some of our discussions here, which population would be at greatest risk, and does that population suffer severe disease from that particular subtype? And so that might also influence where you'd want to de-risk. You know, you'd want to err on the side of caution for an age group, like over 65, or under 3 or something like that. Did that answer your question?

Dr. El Sahly: I guess we'll wait on some committee meeting in the future for that.

Dr. Wentworth: Yeah. I mean there, I think basically there's going to always be times where the ferrets don't quite pull something apart. Or, more often, humans are just very fuzzy because we have so much prior history in our immune response, And very few antigens are given to humans, right? So we can give ferrets every new emerging virus, whereas we can't do that with humans.

Dr. El Sahly: Okay. All right. Thank you. Dr. Portnoy.

Dr. Portnoy: Alright, thank you. I have a comment and then a question for Dr. Wentworth. My comment is that we've been meeting, I've been meeting with this committee for a number of years now, and at the end of the last vaccine committee meeting for the Southern Hemisphere, we sent very strong recommendations to the pharmaceutical companies that they should consider looking at other strains, maybe trying to get a new licensure or modification of the licensure that they have. And it doesn't seem to me like any progress has been made on that. We're still basically allowed to vote on these same four types of questions that we've been voting on all along.

I guess one concern I have is that if we decide to vote no on one of these, let's say number two, we say no. Well, what's the option then? Is there another option that we could vote for? I thought that we have to kind of be in harmony with the whole planet with the WHO. And so if

we say no, there's not really an alternative, we kind of have to vote yes. So I'm not sure that we even are given an option for that. I would kind of like to hear a comment about that.

My question for Dr. Wentworth is, kind of, I asked it before, do you have any information about cell mediated immunity and human responses to influenza? How durable is an immune response to influenza vaccine? Is that dependent on the strain or the individual or what determines that? How long before the flu season should someone get the vaccine and not worry about it wearing off before they actually get the influenza? Do we have information about that?

Dr. Grohskopf: Dr. Wentworth, this is Lisa. I can take that if you like. Is that okay?

Dr. Wentworth: That would be great. Well actually ,I think the first part is for FDA and the second part is for us, but it'd be great if you start on the second one too.

Dr. Grohskopf: Referring to the waning immunity question.

Dr. Wentworth: Yeah, yeah.

Dr. Grohskopf: There are a lot of studies on that currently, and while there does seem to be some waning of immunity, the results sort of depend on a number of things. One is, it seems to be more common among older adults. There aren't as many studies of people at the extreme, other extreme of age, children. And the results are kind of mixed with kids. It seems like it might be more common with H3N2 than with H1N1. It does raise some complications with regard to policy recommendations for timing of vaccination, because as we've seen, sometimes we have early seasons. We did have an early season this season, but it wasn't the first time that that's happened over the last 40 seasons or so, roughly between 1982 and 2021. There was one that peaked in October and one that peaked in November and others that peaked in December. So it’s not unheard of.

So recommendations for timing the vaccination are somewhat made a little tricky by those things. But there, there is general acceptance. I think that there is waning, but it's not seen in every study consistently, and it's not seen cross populations consistently.

Dr. Portnoy: Do these vaccines create cell mediated immunity? Do you know?

Dr. Wentworth: Yeah, maybe I can, I can chime in there on the cell mediated piece, unless Lisa wants to. Okay. So yes, they do. And the natural infection creates cell mediated immunity. And as you're clearly aware, cell mediated immunity is kind of a much trickier thing to analyze in a high throughput fashion. There's a number of extraordinarily funded investigators from the US government, primarily through NIH, as well as many other investigators globally that study T-cell recognition of influenza viruses. And so cell mediated recognition, but by, primarily through T-cell recognition.

And the way that's working is many small peptides of every protein of the virus are really generated to make T-cell recognition epitopes, and some more prevalent than others. And flu does actually slowly mutate to evade those, you know, some of the primary ones. But really, when you consider cell mediated immunity, most of what flu is doing at that annual level is in response to antibody mediated immunity. And so that the cell mediated piece is, I'm not trying to discount it, because obviously it's an important arm of our immune system and likely pays a big role in protection from severe disease and clearance of infection. So after the acute phase of infection, you know cytotoxic T-lymphocytes and T-helper cells are really important in generating new killing off virus infected cells and general generating new. Antibodies through T-cell help and things.

But anyway. When it comes to the vaccine part selecting antigens, what I showed you is that HA molecule. 566 amino acids. Three or four are different. Six are different, right? This is

not going to kill off a T-cell response, right? You see what I mean? So this is why the updates are primarily driven, because what we're trying to do is protect people from infection and then symptomatic disease and then, of course, severe disease. And so the short of it is, a lot of the T-cells will work regardless of which antigen we select.

Dr. Portnoy: Okay.

Dr. Wentworth: You know, they'll get stimulated and boosted by almost any antigen we pick. There might be one new prime to something like Darwin, where the linear part of that epitope, which you're seeing in three dimensions, is actually quite different and spurs new T-cell recognition, for example.

Dr. Portnoy: Thank you. And what happens if we vote no on one of these?

Dr. Wentworth: Oh yeah. So that I think is really a question for FDA, and my interpretation would be it's a question of what are you saying? Vote no on a strain antigen selection.

Dr. Portnoy: What if we, what if I don't think that the, A/Darwin/9221 should be used this year? What, why are we being asked to, why are we being asked these questions?

Dr. Wentworth: I'll turn it over to Dr. Weir. And then I may follow up Dr. Weir, because I could add to something maybe.

Dr. Weir: Okay. So yes, we have, maybe I didn't say this at the start. I think I usually do. Generally, we put these out as a starting point, and if the committee should vote no, then I think the committee would have to come up with an option, a proposal for something else to vote on. Might not be that easy, but I think that would be how it would have to work. Because again, these are licensed vaccines with four components. And it's our job to select something. So I think

it would be incumbent upon you, the rest of the committee that voted no, to offer an alternative. Like I said, we usually do this, and we just assume we would deal with it if, if that happens.

Can I make one comment about the T-cell recognition though? Just to throw something out. One of the things that was noted many, many years ago is that particularly a CD8 response to influenza was mostly directed, if not all, directed against internal proteins, which of course, are not in any sort of, are not really included in the current vaccines. And in fact, vaccines that are subunit, that are proteins like this don't actually induce a very good CD8 T-cell response anyway. So it's not that it's not important, it's not, but it's probably a fairly minor component of this type of vaccines. Over.

Dr. Portnoy: Thank you.

Dr. El Sahly: Dr. Bernstein.

Dr. Bernstein: Thank you. I had a question for Dr. Wentworth and one for Dr. Fries. I recall, I think last year, I mean you present such detail and so extensively. It's incredibly impressive. And I remember, I believe last year, and then again this year, that the 5a.1 is lower in the pediatric population. Again, the response, particularly children 6 months through 35 months of age. And I was wondering how does that relate, if at all, to the fact that there's a higher than average number of pediatric deaths, for example? And how should that be considered, if at all?

Dr. Wentworth: Okay. Thank you for that question. Really insightful. So the 5a.1s, the vaccine, of course, which we ruminated more on last time around was 5a.1 versus 5a.2, because the 5a.1s had made a kind of a rebounding effect. But the likelihood, from the committee's perspective and the WHO committee's perspective, was that it was going to decline. And it has declined tremendously. The reason you see that in that age group is because, and this is the case where that age group is a little more like a naive animal model, in that the 5a.1s and 5a.2s are

very energetically distinct to a naive host. But they both come from a 5a background. So they both have the same kind of progenitor viruses. And the 5a.1s circulated prior to the 5a.2s.

And so as you get into the older age groups, they've been either vaccinated and/or infected by 5a and 5a.1 viruses. And that's why when we boost with a 5a.2, lot of those conserved epitopes across them are likely being reactivated. And so we do see neutralization. So that the gist of it is, exactly why we see neutralization, maybe I'm reaching a little bit into immunological memory. That's the most likely scenario. But we see that any of those older age groups now neutralize the 5a.1 viruses as well.

And so then with the pediatric deaths. I don't, we don't actually, don't have the numbers for H3-caused pediatric deaths and H1-caused pediatric deaths this year. Maybe Dr. Grohskopf does. But we had pretty even cocirculation of those two. That's being monitored. What Dr. Grohskopf showed was from the United States where we had an overwhelming amount of 5a.2 viruses. So those pediatric deaths are likely actually not vaccinated. Generally, and we don't get that information, I think, until later in the season, but generally about 80% of the pediatric deaths are non-vaccinated individuals. And so I don't think that the 5a, the loss of recognition in the 5a.1 group was the reason we saw those pediatric deaths. I know they were a mixture of H3 and H1, because we had so much H3 circulating early. And there were some pediatric deaths then. And we didn't have that much in the way of 5a.1 viruses in the United States.

Dr. Bernstein: Thank you. And then I had a question for Dr. Fries. It's not directly related to strain selection. But the question that I had is, you mentioned that, in the military, that flu vaccine is compulsory. And I was wondering whether that included their dependents and children from six months of age on up. And also for those that are, the 6% that are not vaccinated, what exemptions are accepted?

Dr. Fries: Thanks for the question. I can, the first point, no. It is only the active-duty component that is required. So the kids and other dependents are not required. As to the distribution of those 6%, I know there are religious exemptions. I know that there are other people on this call, perhaps a Dr. Badzik, may be able to speak more directly to other exemption components of that. But yeah, I don't know exactly that distribution. I do know that religious and/or… Well, yeah, I guess the only one I can say for a certainty is the religious. And 94% is typical. I've seen higher numbers. I've seen 97% in some of the services, so I'll just state that as well, that they're not always that 6% each year. I hope that helps sir.

Dr. Bernstein: Yeah. Thank you. And do you use, we periodically talk about exploring vaccination history over a number of years looking at different issues. Has the military, the group that since they're getting vaccinated annually and being part of the military, have they been explored as far as the impact of vaccination history?

Dr. Fries: Yeah. Now I do know that that is an active research avenue, and I'll confirm that one of my colleagues just texted and said that it is primarily religious and medical exemptions for the avoidance of the, for that 6%. As to the active research towards vaccination history, as I think I alluded to in the end of my talk is that, yeah, this is an extremely heavily vaccinated, we know all of the, you know, a good portion of the vaccination record. That does offer some insight into, especially in congregate settings, like a Naval Academy situation, where an H3N2 outbreak occurred at the beginning of the 21-22 season. Does offer some unique perspective as to what protection is provided by the vaccines. But as the specific efforts, those are in collaboration with folks at NIH and the CDC in terms of how those heavily vaccinated rates might impact vaccine or sort of antibody generation.

I will say that there have been discussions about, and I don't want to over-speak, and this is purely me, just anecdotally saying that there have been discussions about not vaccinating every year in certain populations to see whether it gets a better response. But there would have to be a tremendous amount of data to support that policy. And I'll just say that people are examining that, and our colleagues at CDC and NIH are helping. Over.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Berger.

Dr. Berger: Thanks. This is a question for Dr. Neumeier, actually. So, Dr. Neumeier, you laid out a really tight timeline for being able to deliver the influenza doses that are going to be manufactured. And you also mentioned that there's a total of around 500 million total doses that are being delivered worldwide. I guess what I'm trying to think about is if, what's the capacity for developing discordance vaccines with whatever is going to be eventually the licensed vaccine and used in order to facilitate some of the research that's needed here to understand the, to generate the evidence base to be able to make a change to the existing licensure?

So what is the capacity to be able to generate those additional doses that would be needed for that? Is the 500 million currently the maximum that you're already at? Is there additional capacity that's needed to be able to facilitate this? I'm just curious what kind of capabilities that industry would have to be able to conduct the clinical research that's necessary here.

Dr. Neumeier: Mm-hmm. Thank you for that question. So the development of a quadrivalent vaccine with a different composition than the licensed one is a development project, similar to the move from trivalent to quadrivalent. So I think I can say that the development will not interfere with commercial production and provision of the volumes that are required in the US market and globally. If we speak about, if I understood your question right, it was primarily

about development, but potentially also about different vaccine compositions in the market. That would be a real challenge. Because in that case, we would have to produce not only four, but potentially five or more components. So I can't, I cannot speculate on those scenarios, but that would be a real challenge, if not impossible.

Dr. Berger: Thanks. and that's kind of what I'm trying to figure out is right now the licensure seems to be that it has to be one H1N1, one H3N2, a B/Victoria, and B/Yamagata lineage. And so what we heard earlier when we were speaking with Dr. Wentworth was we don't really know what the proper composition is going to be at the end of the day. And so there might be a need to generate different types of vaccine compositions to be able to have, at least in my mind, a licensure that could allow for greater flexibility in being responsive to whatever virus happens to be circulating. It is likely going to be the most impactful for any given season. So I'm trying to understand like, what's the clinical research side of this look like and how much can you actually, are you able to respond to be able to develop that? So thank you.

Dr. Neumeier: Well, as I said, the development would be comparable to the development of the quadrivalent after the trivalent vaccine. So we would have to generate, first of all, the analytical tools to analyze two closely related, antigenically distinct, but still closely related H3 components, for example. Then, preclinical and clinical data would be needed to find out whether there is any type of interference between the different components to make sure that the immune response to all the components is there. It was mentioned earlier today already that it is conceivable that if two H3 components are included in the vaccine, the immune response would be predominantly directed to the conserved epitopes and not to the epitopes that have changed during antigenic drift. So all these things, we don't know them today, and they would have to be

part of the research program to develop a vaccine with a different composition than the one we have today.

Dr. Berger: Thank you.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah, I had a couple of questions for Dr. Wentworth. One of these may be one that was answered many, many years ago. But when one changes the composition of the vaccine and puts in a new antigen that's slightly different, so recognizing the changes, do you have a sense in how much of the immune response actually responds to the new antigens as opposed to the conserved ones, which we've talked about extensively?

Dr. Wentworth: Yeah, that's a good, great question. No, I don't have a direct answer. I mean, I think what I would say is you don't get a huge prime to the new epitope. You get a prime to the new epitope, but you do get a good boost to epitopes that are cross neutralizing between the new antigen and what you've seen previously. And that's evident when you look at those serology panels. You do see, when we change antigens, so like when we changed to Darwin/6 the first time, though there was a good prime against Darwin/6, it was the highest titer response. So you're more of an immunologist than I am, frankly. And so I would say that that's telling you that you are seeing some priming effect.

I think it's different. It's not always the same. Like some years we may not get as much prime as we would like to the new antigen. And it's likely dependent upon kind of your exposure history, so certain age groups and what they've seen in the past and things like that.

Dr. Perlman: The other question I had is when, you have such a huge database now, which is really great. It, do you, with the new mutations that arise in either the H3N2 or the H1N1, can

you go back like 10 years or 20 years, do those same mutations, were they there and then disappeared? Or these all new mutations, all the time?

Dr. Wentworth: Yeah, yeah. This is a great question, and yeah. You can actually do this yourself now as a lot of the data is existing in from the database can be displayed in GIS8 or in NextStrain up to about 12 years. And what you'll see is, if you start really looking at certain positions, you'll see the same position changing and rolling, what I call rolling forward. So it would go from an isoleucine to a phenylalanine to a serene, or something. So you'll see it change forward. You won't, you'll rarely see it ever go backwards unless, it kind of did when we went from seasonal H1N1 to pdm09 H1N1. And that's, I think, really a testament to what population immunity always drives. You know, even though that's a very hotspot, a hot position for mutation that is impactful, it will change to something new rather than flip back. And so that's just a general thing.

Other times, it's the context of the current hemagglutinin, so it's not always the same position. So there's seven positions that Smith et. al, Derek Smith's team, actually published quite a while back now that really, we know are important in the various epitopes, primarily A and B. But there's also the context of the current hemagglutinin sometimes puts a position to have a huge antigenic impact, when in the past it really hasn't ever been used and it hasn't had much of an impact, or it's been there and then just kind of died off, like just in a small number of virus and never gained traction. And so either that mutation, while it is causing antigenic escape, it causes fitness loss in receptor binding or some other feature, Or it's the new context of all the other mutations that are surrounding the area that's allowing that change to make a difference.

Dr. Perlman: Okay. Thanks David.

Dr. El Sahly: Dr. Chatterjee.

Dr. Chatterjee:Thanks, Hana. My question is for Dr. Neumeier as well. I am curious about those 300 million doses that go elsewhere besides the United States. Are you able to share that information with us?

Dr. Neumeier: In a general way, certainly. So most manufacturers that that supply, or all manufacturers that supply the US, also supply other markets in the world. And that may be different from manufacturer to manufacturer. So I think that's all I can say.

Dr. Chatterjee:Okay. Thank you.

Dr. Neumeier: Unless you have a specific question.

Dr. Chatterjee:No, I was just wondering, because it seems like a pretty significant proportion of the total number of doses that are that are made available. And while the US population is definitely pretty significant, there are other large population centers in other countries. And I was curious whether these manufacturers supply, for example, the Russian market or the Chinese market and things like that.

Dr. Neumeier: Yeah. I'm afraid I cannot comment on that.

Dr. Chatterjee:Thank you.

Dr. Neumeier: But in Russia or China, because you mentioned these examples, there are also several local manufacturers that supply these markets.

Dr. Chatterjee:That's what I thought would be the likely answer. Thank you.

Dr. El Sahly: Thank you. So quick question, I guess to the FDA, and to a degree to Dr. Wentworth. So the complications of having two H3s, two H1s, et cetera. I mean, the moment I start thinking about all the permutations and what potentially can go wrong in terms of interference, et cetera, it's a complicated process. But we do have evidence that B/Yamagata is no longer posing health threat to the public. And that we also have a reassurance in the back of

our mind that, to a degree, the B/Victoria does cross-react with the B/Yamagata. So not all would be lost should Yamagata rear its head again. The amount of developmental research that needs to go in removing Yamagata, I presume, is not there. It's not a high list kind of thing. So what, in your opinion would be the downside of removing Yamagata now from the vaccine?

Dr. Weir: Was that to me or to David or both of us?

Dr. El Sahly: Let's begin with you. I'll allow David a breather.

Dr. Weir: Okay. I'll start. But I think some of it's been covered. The downside, of course, is that the lack of certainty that that strain of the Yamagata has really, no longer exists. And you know, you just saw some of the slides that said that only a very small proportion of the B isolates were really typed. So there is some downside to taking it out too early. I think that was your primary question. The other downside of taking it out is that, and I kind of stressed this earlier, I think, if it's going to be… Okay, so from a regulatory point of view, it can be taken out. That part is actually hard because manufacturers are licensed to produce trivalents or quadrivalents.

Dr. El Sahly: Yeah.

Dr. Weir: The real issue is coordination, though. I don't think you're going to see one manufacturer just decide to take it out by themselves because then they will say, well, how does this play in the public? How is this going to be marketed when everybody else keeps four? So that's back to the whole issue of, if it's going to be taken out, it probably needs to be coordinated globally, just for, otherwise it's just not going to happen. Regulatory-wise, yes, we can deal with it. That's not a problem.

I think we've already discussed though, besides the issue of taking it out, there is the issue of coming up with a different composition, and that's the one we've mentioned several times, that there's just got to be some more data generated so that we don't basically do something wrong

with a vaccine and actually have something that doesn't work as well. And I think Elizabeth mentioned the fact, some of the details about, in the development work. There are some issues that can only be solved by developmental research. And that's coming up with potency reagents for two things that are very closely related, coming up with serology reagents for two things that are closely related. It's not that those are insurmountable, that just takes some work. I may have covered most of it, but looks like David can also chime in here.

Dr. El Sahly: So I could not agree more with you on the issue of if we are to choose two H1s or two H, et cetera, or if we advocate for that the amount of research that has to go through before this even begins to become a reality is huge. But the Yamagata question, I feel is separate, that it's been, even pre-pandemic, there was a decline. In the pandemic, there was nothing. In our previous meeting, we indicated, well, let's have another cycle of robust influenza circulation before we can make up our mind. So would it be another season of a similar Yamagata zero, close to zero circulation before we are confident that we probably —?

Dr. Weir: I think you're probably right. And when I talked to Dr. Subbarao who's also I think the chairman of the VCM, this particular time, I talked to her last week, she indicated pretty strongly to me that the WHO intended over the next year to have meetings, both with interested stakeholders, that included manufacturers, to just address these types of issues around the B/Yamagata. When is it going to be, when is everyone going to be comfortable that it no longer exists? Is there more data that we need to be to get to that point? So I did get the strong impression for her that there were going to be follow-ups this year by WHO to address this issue. David, you were at the meeting. You can —

Dr. Wentworth: Yeah, that's exactly right. I mean, so there's a goal to do some follow-ups. There's a goal to do some targeted work in the younger age group in particular. Because they

would be likely the most susceptible, based on population serology type work. But that is also the risk. It's to that age group wouldn't have any prior infection history with Yamagata-like viruses. They wouldn't be… So for example, if we went to a trivalent for that had a B/Victoria, you do get some boosting of the Yamagata responses in older people. But you wouldn't see that in that very young population. It would be just like my answer about the 5a.1s and 5a.2s with the H1, but it would be more striking, because there's many, many amino acid differences between those two lineages. And so that's one of the risks.

What's the benefit, is another question that maybe the committee wants to ask themselves. You know, what's the benefit of removing it if you don't have something else to switch to? And then I think in the trivalent scenario, probably in the US we're okay, but I think there may be some challenges to moving to trivalent in Europe, because I'm not sure their licenses are maintained if they're not continually used. And that would be a question for Dr. Neumeier.

Dr. El Sahly: Okay.

Dr. Weir: And can I add one more thing while I'm thinking about it? You mentioned, and you and David both touched on the cross reactivity. Just remember, back before there were quadrivalents, it was often a real struggle to pick which one of the B lineages to include. And we were essentially wrong about half the time, certainly at least a third of the time. And you could see clinical consequences when that choice was not well matched. So it's, the cross-reactivity doesn't save you. Over.

Dr. El Sahly: Okay.

Dr. Wentworth: Yeah. Thanks for pointing that out, Jerry. I didn't mean it in a way that you would be completely safe by having Victoria in there. I was trying to get at the age

difference. My recollection is some of those times the VE would go down in the twenties when you, when the tri — this was before my time, but when the trivalent was used and say for example, a B/Victoria was selected and we had a B/Yamagata season, or vice versa. So I wasn't trying to say everything would be fine in that respect.

Dr. El Sahly: All right. Well thank you both for sharing this viewpoint. Dr. Pergam.

Dr. Pergam: Yeah. So I had sort of a different question. You know, we've been talking a lot about sort of the vaccines and targeting those specific subtypes, et cetera.

But one advantage of influenzas, we have therapies that actually are effective. And I've been curious that we haven't really seen much transition to oseltamivir resistance strains or baloxavir resistance strain. In these seasons, last two at least, considering for baloxavir, it's very little genetic differences between those that develop resistance. It's maybe a mutation or two that can lead to it. So one of the questions I'm curious maybe Dr. Grohskopf can talk about this from the CDC, or others, is have we seen differences in treatment of those who are influenza positive? And I wonder as we have more Covid testing and more combination testing strategies available for both Covid and flu and RSV for that matter, is that potentially a change that we need to be sort of on the lookout for?

And then as a follow up to that, Dr. Wentworth, can you just clarify sort of how, since there are all of these genetic tests that are done on different strains and there's subtests that are done, can you just clarify how the decisions are made to look for resistance and what percentage, if at all possible, these are done to look for resistance within the strains of particularly Influenza A that we have?

Dr. Grohskopf: For the first part of the question, I'm not aware that we have any particular insight or surveillance on use patterns of the anti-influenza antivirals that are currently in use. We do have guidance for their use, but I'm not aware of any mechanism that we have to monitor changes in practice patterns.

Dr. Perham: Thank you. And then, so towards your second question. So there's a combination of things done. Like we do for antigenic phenotyping, we now use a genotype to phenotype kind of systematic approach, where we're using genetics first and then selecting viruses for phenotyping. And that's true for antigen analysis as well as antiviral susceptibility analysis. And so with the neuraminidase, we can look around the active site for mutations that could impact sensitivity or resistance to like, say for example, oseltamivir-like compounds. Neuraminidase inhibitors, most of them are targeting the active site of the enzyme. And so then we would take those, and we can test them phenotypically. Now often, so for example, in H1s, there's an H275Y substitution. So that's a very specific substitution. And it leads to highly resistant phenotype, or not sensitive phenotype to that particular, to oseltamivir or other drugs that are neuraminidase inhibitors. And so that's a very kind of genetic signature that we almost always know the phenotypic outcome. But in the H3N2, for example, there can be many substitutions in and around the active site. We're not sure if it's really impacting in this particular context. And then we'll test it phenotypically to see if it's considered sensitive or resistant to the compound. And the same is true for baloxavir. We look around where the region where the compound interacts and our… That one we have a lot less experience cause it's a newer drug. But, and we then we go into a phenotypic assay. And for that one, rather than doing an ELLA-based neuraminidase type assay, we use the HINT assay again, which is really looking for the virus replication in the presence or absence of drug.

Dr. El Sahly: Thank you. Dr. Monto.

Dr. Monto: I'm going to take us back to the Yamagata situation. And I just want to remind us all that, in terms of Covid strain selection, because things were not moving quickly at WHO, the US took the decision to make a different recommendation from the one that was made by the WHO advisory group. I don't think we should do that here. I think the flu vaccine is a global, some people would say commodity. And that's part of the problem. I think without moving towards identifying our discomfort with the fact that. We've gone for several years. Granted, we had the pandemic, and everybody has been busy with other things. That we really haven't looked towards some of the solutions to increase VE by including additional strains or even more of the age three and two in a trivalent vaccine. And I feel very uncomfortable at this point in continuing to recommend a B/Yamagata strain. I'm not going to go as far as to vote no, but I will abstain, because I don't feel comfortable in continuing to ignore what looks like a situation where B/Yamagata is no longer circulating. And we're not really trying to figure out what we should do to at least use the same antigenic weight that we have in the current vaccine of 15 micrograms times four to improve to improve vaccine effectiveness. We really need to send a message, and I'm not so sure that's done if it's only private conversations that indicate that something may be brewing, because it needs to include the manufacturers, as well. Over.

Dr. El Sahly: Thank you, Dr. Monto. Okay. I don't see any raised hands. Please use the raise your hand function if you have any final thoughts or comments about flu vaccine strain selection. Okay. Well, question two, Dr. Wentworth. So we didn't have Yamagata for, well, it started going away a little before the pandemic, and then it went away during the pandemic, and during a really heavy flu season, it didn't rear its head yet. I'm going to ask you to use your crystal ball, which we always ask you to use. If it were to come back, would it, like, all of a sudden take

over? Should we expect it to take over? Or maybe allow us time to recalibrate in a subsequent season? I mean, I, it's only one out of four. H3 is always the one that trumps us with morbidity and mortality anyways. I'm not dismissing the others, but I'm trying to put it in context. And in light of what Dr. Monto said, that we should start moving in different directions at one point.

Dr. Wentworth: Well, okay, so I think number one, I would comment to Dr. Monto. I actually agree that we really need to be moving forward and to see what we can do, because it takes a long time to license something new. And so I'm in complete agreement with that. I would say that I think the question here is, which, it's a licensed product for a quadrivalent vaccine that has a B/Yamagata component. So the question is really, do you put Phuket in it, or what else do you put in it? So to me that that's more of an FDA point, but to me that's the way I read these questions.

And then to the crystal ball piece, it entirely depends upon what kind of Yamagata reemerges, if one does. So, there was some very odd-looking B/Yamagata viruses in the Netherlands prior to its not being isolated anymore. Really antigenically distinct. And so if something like that were to reemerge and be fairly fit, it could move through our population in the same, I would guess, the same speed with which the triple deletion B/Victoria viruses moved through our population, which was within about six months, it was a sweep to that whole strain. So that's kind of one vaccine cycle. Now, depending on when that catches us in the vaccine cycle, that could be very bad, or it could be not very bad at all, right? If it looks a lot like the viruses that we saw in 2019 that were kind of the run of the mill, they were very B/Phuket-like antigenically, even though they were quite old. A few years since that virus was isolated. Then, I think they would move relatively slowly, and you would have this kind of petering, you know, with years' time.

And so I think it really depends on what emerges, but I don't think it's out of the realm of possibility that something antigenically quite distinct could emerge. I mean, that's really what you saw with H3 through the Covid bottleneck. You know, something quite distinct eventually kind of really took hold. And so it's not a very much of an answer. It probably doesn't make you feel very better, but you know, I think that's really the case. I mean, you look at B/Victoria, it's swept in about six months.

Dr. El Sahly: Okay. Dr. Monto again.

Dr. Monto: Does that mean, Dave, that whatever we vote for, which is a very old strain, would likely be a mismatch anyway?

Dr. Wentworth: Yeah. Well, if something reemerges, it would be a mismatch given that scenario. It could be, you know, I think the last virus isolated in March of 2020 was kind of antigenically like B/Phuket here. But it could be, if it's something very different, that it is a drifted variant. I think I would still argue that you would be better off with Yamagata if that did happen. You'd be better off with Phuket in there than with nothing. Because as you know, it's still a boost to all your previous Yamagata and some priming to some aspects of it. So that's a great question. Something for the committee to think about.

Dr. El Sahly: One last question from me, David. I don't see any raised hands yet. So we have a, I guess a cohort of our population that's been vaccinated against Yamagata for the last few years with not much exposure and definitely not much virus or drifting or and new antigenic sites to react to. Are we responding well? I mean, are we still seeing some of those cohorts you are following? Are they B/Yamagata?

Dr. Wentworth: Yeah. Yeah. We're seeing pretty good response to Yamagata. We didn't, I didn't show you human serology data, because we did not do a panel of human serology. We did

do a screen of the vaccinees to see that they responded to the Yamagata component. But there's no new emerging variants to test against, so it's kind of pointless to do that.

Dr. El Sahly: But they're responding to the antigen that's in the vaccine despite that?

Dr. Wentworth: Yeah, but they're responding to the antigen that's in the vaccine. Yes. They're responding to the antigen that's in the vaccine. In our quadrivalent vaccines. And that's really the only vaccines we have in our serology testing. So I don't, we don't have a trivalent.

Dr. El Sahly: Okay. Final opportunity for committee members to ask questions, provide comments before the vote. Okay. All right. Thank you all. Dr. Paydar, so do I read, do we display the questions? Do I read the questions again, I'm sorry. Or how should we proceed?

Dr. Paydar: Oh thanks for asking. I'll just go ahead and read the voting script. And then from there I'll have you read the questions one by one. We do it consecutively, and then we will have the final voting explanations all the way at the end. So alright, so let me read the script first. 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 following options, which include yes, no, or abstain. You'll have one minute to cast your vote after the question is read. Please note that once you've cast your vote you may change your vote within the one-minute timeframe. However, once the poll has closed, all votes will be considered final. Once all the votes have been placed, we will broadcast the results and read the individual vote aloud for the public record. I'm going to ask if anybody has any questions regarding the voting process before I begin. If no, okay. Dr. El Sahly, if you would be kind to, please go ahead read the voting question number one for the record.

Voting Question #1

Dr. El Sahly: Voting question one. For the influenza A (H1N1) component of the 2023-2024 influenza virus vaccines in the US, does the committee recommend: an A/Victoria/4897/2022 (H1N1)pdm09-like virus for egg-based vaccines and an A/Wisconsin/67/2019 (H1N1)pdm09-like virus for cell- or recombinant-based vaccines?

Dr. Paydar: Great. Thank you. At this point Joseph will move all non-voting members out of the main room. For those of you who are non-voting, please stay tuned. Please don't log out of the Zoom. We'll be back in a few. Joseph, let me know when all the voting members are present. Thank you. All right. Opening up breakout room now.

Dr. Paydar: I will now read the results for the for the public record. Dr. Hayley Gans, yes. Dr. Hana El Sahly, yes. Dr. Jay Portnoy, yes. Dr. Steven Pergam, yes. Dr. Stanley Perlman, yes. Dr. Arnold Monto, yes. Dr. Paul Offit, yes. Dr. Douglas Badzik, yes. Dr. Archana Chatterjee, yes. Dr. Amanda Cohn, yes. Dr. Holly Janes, yes. Dr. Adam Berge, yes. Dr. Hank Bernstein, yes. Okay. Hana, if you would be so kind to read question number two for so we can go ahead and vote on that one.

Voting Question #2

Dr. El Sahly: For the influenza A (H3N2) component of the 2023-2024 influenza virus vaccine in the US, does the committee recommend: an A/Darwin/9/2021 (H3N2)-like virus for egg-based vaccines and an A/Darwin/6/2021 (H3N2)-like virus for cell- or recombinant-based vaccines?

Dr. Paydar: So for voting question number two, again, we have a unanimous vote. 13 out of 13 members have voted yes. And I'll read the names for each of the votes for the public record.

Dr. Steven Pergam, yes. Dr. Adam Berger, yes. Dr. Haley Gans, yes. Dr. Archana Chatterjee, yes. Dr. Arnold Monto, yes. Dr. Paul Offit, yes. Dr. Hana El Sahly, yes. Dr. Jay Porto, yes. Dr. Amanda Cohn, yes. Dr. Stanley Perlman, yes. Dr. Hank Bernstein, yes. Dr. Holly Janes, yes. And Dr. Douglas Badzik, yes. Hana, if you would be kind to read the third voting question for the public record.

Voting Question #3

Dr. El Sahly: Voting question three. For the influenza B component of the 2023-2024 trivalent and quadrivalent influenza virus vaccines in the U.S., does the committee recommend inclusion of a B/Austria/1359417/2021-like virus, B/Victoria lineage?

Dr. Paydar: All right, we are ready to share. Okay, great. Thanks, Joseph. Again, we have 13 members who voted yes for voting. Question number three. It was a unanimous vote, and now I'll read the votes for the public record. The official votes. Dr. Archana Chatterjee, yes. Dr. Paul Offit, yes. Dr. Jay Portnoy, yes. Dr. Hayley Gans, yes. Dr. Stanley Perlman, yes. Dr. Amanda Cohn, yes. Dr. Hank Bernstein, yes. Dr. Steven Pergam, yes. Dr. Adam Berger, yes. Dr. Holly Janes, yes. Dr. Douglas Badzik yes. Dr. Hana El Sahly, yes. Dr. Arnold Monto, yes. Okay. With that, we will move to our final voting question, voting question number four. Dr. El Sahly, if you could please read the question for us?

Voting Question #4

Dr. El Sahly: For quadrivalent 2023-2024 influenza vaccines in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus of a B/Yamagata lineage as the second influenza B strain in the vaccine?

Dr. El Sahly: We are ready to display. Great. Thank you. Okay. We have 13 Voting members for voting question number four. 7 out of 13 have voted yes. 2 out of 13 have voted no, and 4 out of 13 have abstained from voting. Now, with that, I will read individual votes for the public record. Okay. Dr. Archana Chatterjee, yes. Dr. Hayley Gans, yes. Dr. Adam Berger, no. Dr. Jay Portnoy, yes. Dr. Stanley Perlman, abstain. Dr. Paul Offit, no. Dr. Amanda Cohn, yes. Dr. Arnold Monto, abstain. Dr. Hank Bernstein, yes. Dr. Steven Pergam, yes. Dr. Holly Janes, abstain. Dr. Douglas Badzik, yes. Dr. Hana El Sahly, abstain. Okay. This concludes the voting portion for today's meeting. I'll hand the meeting back to Dr. El Sahly for asking the committee for the vote explanation. Thank you so much.

Voting Explanations

Dr. El Sahly: Thank you. Thank you, Dr. Paydar. So to start us off, I see a raised hand from Dr. Weir. Dr. Weir.

Dr. Weir: Yes. I'm sorry to have to say this. There was a typo in question number one. The second part of it, the Wisconsin, should have been 67/2022, not 2019. So I'm not sure what we need to do about it, but I thought I better point it out now rather than later.

Dr. El Sahly: Should have given it a different name, right? Would've been much easier.

Dr. Weir: We looked at this at least a dozen times.

Dr. Paydar: Don't worry about it, Dr. Weir.

Dr. Weir: Okay.

Dr. Paydar: We'll adjust the writing, and we'll resubmit it when we web-post the final. It's okay. We'll adjust at that point. As long as the committee is comfortable with the voting, based on the current information, we should be okay.

Dr. Weir: Okay. Thank you.

Dr. Paydar: No worries. Yes.

Dr. El Sahly: The committee wants the strain displayed by Dr. Wentworth. Okay. So I'm going now to go over the virtual table and request that the committee members provide the rationale for their votes as briefly or as expansively as you wish. And I'm going to go in the order that the names appear here on my screen, and I think it's Dr. Berger.

Dr. Berger: Two weeks in a row, I get to do it first . So, but at least it's just one explanation. I'm going to skip my, my votes for questions one through three. I think those are self-explanatory as to why those are needed components of the vaccine. So I'll say I voted no one the last question around the inclusion of B/Yamagata for the same reason I voted no in the last meeting. The inclusion of a strain that's not circulating doesn't seem to offer additional protections for the public. And this isn't to vote against continuing the currently licensed quadrivalent, but at this point I think we really need to send a strong signal that, in the interest of public health, we need to be conducting the studies to generate the evidence base for a much more flexible vaccine composition now. So that's the reason why I voted no. That's it. Thank you, Adam. Dr. Cohn.

Dr. Cohn: Great, thank you. I will also skip my first three votes, which were yeses. I voted yes for the fourth vote to include the Yamagata because, even though I completely agree with Dr. Berger's points, I did have concerns about what would happen to the quadrivalent vaccine and the program if we didn't have a usable vaccine for this year. And so in the spirit of ensuring that we had accessible choices of vaccines while we continue to move forward with improving those transfer in there. I voted yes.

Dr. El Sahly: Thank you, Dr. Cohn. Dr. Chatterjee.

Dr. Chatterjee:Thank you, Dr. El Sahly. So I will follow in the footsteps of my co-committee members and not explain my yes vote for the first three questions. I basically looked at the data that were presented and it seemed reasonable to include those three strains. With regard to the B/Yamagata, I've given it a fair bit of thought, and I do not disagree with the comments already made. I do think, though, that the concern that Yamagata may reemerge, the fact that a large proportion of the B strains were actually not subtyped, so we don't know exactly what they were, were concerning to me. One other thing I will say with regard to including a strain that does not appear, at least from the data we have at hand, to be circulating at this time is something that I haven't brought up before but has been in the back of my mind. And that is, including an antigen that doesn't perhaps provide any benefit and yet certainly has some element of risk, although it might be minimal attached to it, but mostly the expense that it involves to grow up those viruses, to get those viruses ready, through recombinant mechanisms, and to have them available for using the quadrivalent vaccine. So I was really torn in trying to decide between those two things.

And I came down on the side of being prudent and cautious and voted yes. Because I do think that probably a little more time is needed to make those decisions. But I would echo my co-committee members' comments about the powers that be working on trying to remove Yamagata from future vaccine compositions.

Dr. El Sahly: Thank you, Dr. Chatterjee. Dr. Monto.

Dr. Monto: I think I explained previously what I was going to be doing. It even if we voted no, we're only advisory, and the staff could be moving ahead with the global recommendation, and it really would have very little effect this year. However, we've waited a long time for some action about a questionable choice to continue with B/Yamagata I disagree with some of the opinions we've heard. The evidence for the need for the quadrivalent is mixed. And there are a

number of studies which were conducted when both vaccines were being used in the United States, which showed very little benefit, at least in an adult population. I think the evidence in children may be different, and perhaps at that time the data were not sufficient to really observe the need. But I think we really need to move ahead on this. We are giving vaccines which have good benefit, not great benefit, and we need to do everything we can to improve the vaccines. And one of the things we know does improve the vaccines is giving more antigen. And we should give the right antigen. Over. Thank you, Dr. Monto.

Dr. El Sahly: Dr. Wentworth. Oh, you're non-voting. I'm sorry, Dr. Badzik.

Dr. Badzik: Yeah. Good afternoon, everybody. So, hang on a second. I have a video to kick on here. So kind of as the rest of the group, as you know, previously stated, I'm not going to go over my reasons for voting yes for the first three, because I think it's self-evident. I did kind of struggle with voting on the fourth one. I ended up casting a yes vote for that, mainly because I didn't really see an alternative. There wasn't an alternative provided. That being said, I think that going into the future, it has been stated previously, I think it's important just not to go and maintain the course unless there's data to support that.

I'm a bit concerned, as you know, we come out of the pandemic, and we see the increasing fervor of the anti-vaccine crowd. And I'm concerned that if we just continue to maintain this this lineage in the quadrivalent without data to back that up, that type of behavior I think could be misconstrued by some in the anti-vax movement just to further the cause. So I, once again, I voted yes, but I would encourage the manufacturers and those that are collecting that surveillance data to do what we can to justify that for next year.

Dr. El Sahly: Thank you, Dr. Badzik. Dr. Gans.

Dr. Gans: Hi. Thank you. I guess we're all sort of leaning towards explaining our vote for the fourth question here, since we were in agreement with the other ones, and there was lots of data to support it. So, I just want to echo that I voted yes. And the reasons I did that are not because I would like to downplay what others had said. There's definitely data to support us moving in a different direction. And I just wanted to echo, I guess, what Amanda Cohn said, that really reflected on me as the sort of global stage and what we need to do to actually keep the global populations healthy. And not necessarily understanding fully what's going to happen as we all recover from the pandemic and not seeing strains. And maybe there has been some immunity that hasn't been boosted over that period of time.

So I voted yes for that to maintain stability, but really, as my remarks in the past have said, really do urge further studies, not only just for this particular strain, but actually to have some ability to be more flexible in general about the strains at which we actually need to vote on, because this issue may come up again. So while this one is current, it will be a different one next time. And so I just would love some flexibility to respond better to the data.

Dr. El Sahly: Thank you, Dr. Gans. Dr. Bernstein.

Dr. Bernstein: Thank you, Dr. El Sahly. I agree with my colleagues around the virtual table about questions one, two, and three. The issue about number four, I voted yes. And in part, that's why I asked Dr. Weir during his introduction right at the beginning, and to me, his response suggested to me that change was not possible for this particular season. And so that being said, it's not clear to me what precise data are needed and during what timeframe this will happen in order to make such a change, which scientifically seems to make a lot of sense. And so I also didn't want that the public to interpret that the quadrivalent flu vaccine is not necessary, because I think that it's important to get as many people vaccinated against influenza as possible. Over.

Dr. El Sahly: Noted. Thank you, Dr. Bernstein. Dr. Janes.

Dr. Janes: Thank you. I'll skip to my vote for the fourth vote, and I abstained from this vote. You know, similar to the reasons have been stated before, basically I felt that there wasn't adequate data given the absence of, apparent absence of, circulation of the B/Yamagata to make a recommendation as to strain selection. And so I hoped that voting abstain would convey the inability in my mind to make a determination. But I fully support the messages that others have put forward around the continued importance of vaccination and that my vote doesn't call into question the importance of vaccination.

I also wanted to second Dr. Gans's comment and request for additional flexibility in terms of how this committee considers the strains that are included in the vaccination in future meetings. Thank you.

Dr. El Sahly: Thank you, Dr. Janes. Dr. Portnoy.

Dr. Portnoy: Great, thank you. Yes, in terms of questions one, two, and three, again, I voted yes, and I'm okay with those even with the error, the typographical error. So it's not a problem. I voted yes for the Yamagata strain. Not because I think that there's a lot of that, but I don't know, does extinct really mean extinct? The 1350, the Black Plague in 1350 was extinct, and 10 years later it came back. So we don't really know for sure that things like that aren't going to return. Besides if we don't, if we vote no for the Yamagata strain, there aren't really a lot of B strains out there. It's not clear that we even need B strains in the influenza vaccines at all.

So I voted for that just because I'm not sure that it's extinct. But I do want to comment on, though, is that I'm hoping that in the future we will start seeing use of more advanced technologies than these legacies like cellular vaccines or egg-based vaccines. We're injecting eggs with influenza virus and extracting it. That's a very old-fashioned technique. I'm looking

forward to the messenger RNA-based influenza vaccines that not only could be modified very quickly as the strains of influenza modify but could also possibly induce more of a cellular immunity, which I think for long-term benefit could be quite helpful. So I'm hoping that's going to be a possibility. We allow the Covid vaccine to have variants in its strain without having a whole new licensing thing. I don't know why we can't take an influenza, license it for just flu, and then make all of the modifications depending on what strains are present that year. I think a newer technology would allow that to happen, and I look forward to that happening in the future. Thank you.

Dr. El Sahly: Thank you, Dr. Portnoy. Dr. Offit.

Dr. Offit: Yes. Thank you. I, like Dr. Berger, voted no. Because I think that if you're going to inject someone with a biological agent, even if it's only one component of a multi-component product, there should be clear evidence for benefit. I don't think we have any evidence for benefit with this strain, and although I agree that this strain may come back in the near or distant future, that is not a compelling enough reason for me to include it now. Plus, I agree with Dr. Monto's comment that, should it come back, you wonder whether or not it would be distant enough from the current strain as to be of value. So I voted no. Thank you.

Dr. El Sahly: Thank you, Dr. Perlman.

Dr. Perlman: Yes, I think it's going close to the end here. I don't have very much new to say. I think that there's not evidence for including Yamagata. I voted, I abstained, because I thought there wasn't great evidence for including it, and because of where we are in the course of vaccine development. I felt that for this year, it would be okay to include it. I didn't vote against it for that reason. And I hope that next year we don't have the same discussion. I hope that there's either

more data saying we should include it, or we have data showing that we should remove it and have removed it.

Dr. El Sahly: Thank you. Dr. Pergam.

Dr. Pergam: Thanks, Dr. El Sahly. I don't have much to add from what my colleagues have already talked about, but I voted yes because it felt like the strain had already left the station related to the quadrivalent. I don't feel like we can do a trivalent international. At least from what was responded, that's a little harder to do. And I think it's important that the process has sort of already begun in some ways within the world stage. But I think I voted yes with sort of a little bit of trepidation because, I think, as others have commented, it doesn't feel like Yamagata is getting us a lot of benefit. What I think we'd all really like to see as additional data and studies planned for what would be a potential replacement for the B strain, if it is removed. So I encourage the FDA to start working with companies to start coming up with those studies to deliver, identify how that might be advantageous for future vaccines.

Dr. El Sahly: Thank you. I think it's my turn. So I abstained from voting on the inclusion of B/Yamagata. I hesitated between the no and then abstain. But it's definitely not a yes. Influenza virus is not known to be shy. If it was going to circulate in the last four years, we would've picked it up. We do note that the trend preceded the pandemic. And we indicated for, I think two or three meetings now, that, well, the non-pharmacological measures of the pandemic are going over. We're seeing a whole lot of flu, but we're not seeing the Yamagata. We said we'd give it one more season. This season was this year, and we had really an abundant circulation of flu all over the world. And Yamagata did not rear its head. When and if it does, we'd be ready.

From a regulatory standpoint, going from four to three shouldn't be a hurdle, because there is a trivalent vaccine. And no additional research or developmental work needs to happen

for us not to include the Yamagata. And when it comes to implementation and vaccine distribution, also not including the Yamagata should not impact our ability to distribute the vaccine to those who need it each year. So that's why I chose not to vote for the Yamagata this year.

I think we are done with the task that that was given to us. Any final comments from the FDA? Or Dr. Weir, Dr. Kaslow?

Adjournment

Dr. Paydar: So for the closing comments, I just wanted to thank the committee and CBER staff for working so hard to make this meeting a successful meeting. We're very grateful for your presentations and for your input. I'll call the meeting officially adjourned at 3:27 PM Eastern Time. Have a wonderful rest of your evening. Bye-bye.