Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

183rd Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

October 5, 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.

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Chair

Hana M. El Sahly, M.D.	Professor, Department of Molecular Virology and Microbiology, Department of Medicine Section of Infectious Disease, Baylor College of Medicine	Houston, TX

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Hayley Gans, M.D.	Professor of Pediatrics, Stanford University Medical Center	Stanford, CA
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Andrea Shane, M.D., M.P.H., M.Sc.	Professor of Pediatrics, Emory University School of Medicine	Atlanta, GA

Temporary Non-Voting Member

David Wentworth, Ph.D. (Speaker)	Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Director, Coronavirus and Other Respiratory Diseases, Centers for Disease Control and Prevention	Atlanta, GA

Industry Guest Speaker

David Greenberg, M.D.	Global Senior Expert Medical Strategy, Vaccines, Sanofi	Swiftwater, PA

Industry Representative

Paula Annunziato, M.D.	Senior Vice President ID and Vaccines, Global Clinical Development, Merck	North Wales, PA

Consumer Representative

Jay Portnoy, M.D.	Professor of Pediatrics, Medical Director of Telemedicine Section of Allergy, Asthma and Immunology, Children's Mercy Hospital	Kansas City, MO

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David C. Kaslow, M.D.	Director, Office of Vaccines Research and Review, Center for Biologics Evaluations and Research, Food and Drug Administration	Silver Spring, MD
Jerry Weir, Ph.D. (Speaker)	Director, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluations and Research, Food and Drug Administration	Silver Spring, MD
Sudhakar Agnihothram, B.Pharm., Ph.D.	Acting Senior Advisor to Office Director, Office of Vaccines Research and Review, Center for Biologics Evaluations and Research, Food and Drug Administration	Silver Spring, MD
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Contents

Call to Order and Welcome

Dr. El Sahly: Good morning, everyone. I would like to welcome the committee members, the participants, and the public to the 183rd Vaccine and Related Biological Products Advisory Committee meeting. Today, we will be discussing the strain selection for the flu virus vaccines 2024 Southern Hemisphere Influenza season. To start us off, the designated federal officer of the meeting, Dr. Sussan Paydar, will go over administrative announcements, roll call, and conflict of interest statements. Before we do that, one reminder to my committee members, colleagues, to use the raise your hand function in Zoom in order for me to be able to see who has a question or a comment, and I can call on you. And now I turn it over to Dr. Paydar.

Administrative Announcements

Dr. Paydar: Thank you, Dr. El Sahly. Good morning, everyone. This is Sussan Paydar, and it is my great honor to serve as the designated federal officer for today's 183rd 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 strain selection for the Influenza virus vaccines for the 2024 Southern Hemisphere Influenza season. Today's meeting and the topic were announced in the federal register notice that was published on August 24, 2023.

At this time, I would like to acknowledge outstanding leadership of Dr. Peter Marks, Director of Center for Biologics Evaluation and Research, Dr. David Kaslow, Director of Office of Vaccines Research and Review, Dr. Weir, Director of Division of Viral Products at 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 for her excellent leadership and my team whose contributions have been critical for preparing today's meeting, Ms. Valerie Vashio, Ms. Joanne Lipkind, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to Mr. Joseph Ely in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one, like all the previous VRBPAC meetings. Please direct any press media questions for today's meeting to FDA's Office of the Media Affairs at fdaoma@fda.hhs.gov.

The 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 member when it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name institution and areas of expertise. And when finished, you can turn your camera off. So, we can proceed to the next person. Please see the member roster slides, in which will begin with chair Dr. Hana El Sahly.

Roll Call and Committee Introductions

Dr. El Sahly: Good morning, Hana El Sahly. I'm at Baylor College of Medicine. I'm an adult infectious diseases physician, and my research is in clinical vaccine development.

Dr. Paydar: Right. Thank you. Dr. Paula Annunziato, our industry representative.

Dr. Annunziato: Good morning. My name is Paula Annunziato. I'm the head of the ID and Vaccines Global Clinical Development at Merck. And I'm the non-voting industry representative for today's meeting.

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

Dr. Bernstein: Good morning. My name is Hank Bernstein. I'm a Professor of Pediatrics at the Zucker School of Medicine at Hofstra Northwell. I'm a General Pediatrician with expertise in vaccines.

Dr. Paydar: Great. Thank you. 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 Rosalind Franklin University in North Chicago. I am a Pediatric Infectious Diseases Specialist with a focus on vaccines.

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

Dr. Cohn: Good morning. I'm Dr. Amanda Cohn. I'm a pediatrician at the Centers for Disease Control and Prevention at the National Center for Immunizations and Respiratory Diseases, where I work on vaccine preventable disease, epidemiology, and policy.

Dr. Paydar: Great, thank you. Dr. Haley Gans.

Dr. Gans: Hi, I'm Haley Gans, a professor of pediatrics and pediatric infectious disease at Stanford University Medical Center, and my area of expertise is on vaccine immunology.

Dr. Paydar: Thank you. Dr. Holly Janes.

Dr. Janes: Good morning. I'm Holly Janes. I'm at Fred Hutchinson Cancer Center in Seattle. I'm a biostatistician by training and my expertise and focus is in vaccine evaluation.

Dr. Paydar: Right. Thank you. Dr. Arnold Monto.

Dr. Monto: I'm Arnold Monto. I'm at the University of Michigan School of Public Health, where I work on the epidemiology and prevention of respiratory infections, particularly vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Monto. Dr. Paul Offit.

Dr. Offit: Yes. Good morning. My name is Paul Offit. I'm a pediatric infectious disease specialist at Children's Hospital of Philadelphia. And my expertise is in mucosal vaccines and vaccine safety. Thank you.

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

Dr. Pergam: I'm Steve Pergam. I'm an adult infectious disease physician at the Fred Hutchinson Cancer Center. And my expertise is on immunosuppressed individuals, particularly bone marrow and immunological patients.

Dr. Paydar: Right. Thank you. Next is Dr. Stanley Perlman.

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

Dr. Paydar: Thank you. 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, and I'm an allergist immunologist at Children's Mercy Hospital in Kansas City.

Dr. Paydar: Thank you. Next is Dr. Eric Rubin.

Dr. Rubin: Hi, I'm Eric Rubin. I'm an adult infectious disease physician at the Brigham and Women's Hospital and Harvard Medical School and Harvard TH Chan School of Public Health and the New England Journal of Medicine.

Dr. Paydar: Thank you. Dr. Andrea Shane.

Dr. Shane: Hi, good morning. I'm Andy Shane. I'm pediatric infectious diseases at Emory University and Children's Healthcare of Atlanta and my area of interest and expertise is in vaccine epidemiology. Thank you.

Dr. Paydar: Great. Thank you. Next, we'll do a roll call of our temporary non-voting member, Dr. David Wentworth.

Dr. Wentworth: Good morning. This is Dave Wentworth. I'm the Director of our WHO Collaborating Center and the National Influenza Center for the US at the CDC in Atlanta, Georgia.

Conflict of Interest Statement

Dr. Paydar: Great. Thank you Dr. Wentworth. Thanks everyone. We have a total of 15 participants, 13 voting and two non-voting members. Now, I'll proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, October 5th, 2023, for the 183rd 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 chair for today's meeting. Today on October 5th, 2023, the committee will meet in an open session to discuss the strain selection for the Influenza virus vaccines for the 2024 Southern Hemisphere Influenza season. This topic is determined to be a particular matter involving specific parties, PMISP. With the exception of the industry representative member, all standing and temporary non-voting members of VRBPAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws including, but not limited, to 18 USC Section 208 is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGE and SGE consultants of this committee, have been screened for potential financial conflict

of interest of their own. As well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 US Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. The 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 US Code Section 208, Congress has authorized FDA to grant the waivers to special government employees and regular government employees for financial conflicts of interest when it is determined that the agency's need for special government employee services outweighs the potential for a conflict of interest created by the financial interest involved. Or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee. Based on today's agenda, all financial interests reported by committee members and consultants, no conflict-of-interest waivers have been issued under 18 US Code 208 in connection with this meeting.

We have the following consultants serving as a temporary non-voting member and speaker for this meeting: Dr. David Wentworth. Dr. David Wentworth is employed by the Centers for Disease Control and Prevention, is the Director, WHO, Collaborating Center for Surveillance, Epidemiology, and Control of Influenza. He's also the Director of Coronavirus and Other Respiratory Viruses Division, CORVD, at CDC. Dr. Wentworth is an internationally known expert in Influenza virus epidemiology, worldwide Influenza disease burden, and Influenza virus vaccines. Dr. Wentworth is a regular government employee and has been screened for conflicts of interest and cleared to participate as both a speaker and as a temporary non-voting member for

today's meeting. Disclosure of conflicts of interest for speakers follows applicable federal laws, regulations, and FDA guidance. As a speaker and temporary non-voting member, Dr. David Wentworth is not only allowed to respond to the clarifying questions from the committee members, but also authorized to participate in committee discussions in general. However, he is not authorized to participate in committee voting process.

Dr. Paula Annunziato of Merck will serve as the industry representative to this committee. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee.

Dr. Jay Portnoy is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee.

The industry guest speaker for today's meeting is Dr. David Greenberg, Global Senior Expert, Medical Strategy, Vaccines, Sanofi, Swiftwater, Pennsylvania. Disclosure of conflicts of interest for speakers, guest speakers, and responders follows applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement and their exclusion will be noted for the record. This concludes my reading of the conflicts of

interest statement for the public record, at this time I would like to hand over the meeting to Dr. El Sahly. Thank you.

Dr. El Sahly: Thank you, Dr. Paydar. To kick us off, Dr. Jerry Weir, Director of the Division of Viral Products at the Office of Vaccine Research and Review at CBER FDA, will go over introductions to the meeting 2024 Southern Hemisphere Influenza Virus Vaccines Strain Selection. Dr. Weir.

Introduction: 2024 Southern Hemisphere Influenza Virus Vaccine Strain Selection — Dr. Jerry Weir

Dr. Weir: Thank you, Dr. El Sahly. Yes, I will give just a very brief introduction to the meeting today and the agenda. This is a brief summary of the agenda today, but after my introduction, you will hear about global Influenza virus surveillance and characterization. This is presented from the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, as we usually hear. But in addition today, we'll also have a discussion topic, the title of which is Challenges and Opportunities for Vaccine Strain Composition with the Reduced Public Health Threat from Influenza B/Yamagata Lineage Viruses. As part of that discussion, we'll hear short presentations from manufacturer's representative, as well as an FDA perspective, and then we will follow with committee discussion and voting.

Okay, so the purpose of today's meeting. The first purpose is to make recommendations for the strains of Influenza A, both H1N1 and H3N2, and Influenza B viruses to be included in the 2024 Southern Hemisphere formulation of Influenza vaccines licensed in the United States. The reason for this is since 2016, we have had two US vaccine manufacturers that have been approved to produce Southern Hemisphere formulations of their Influenza vaccines. These are Sanofi flu zone and Seqiris Afluria. Both of these vaccines are quadrivalent and both of them are

produced in eggs. Our procedure, our strain recommendation, and supplement approval for Southern Hemisphere formulations, follows the Northern Hemisphere process, and we use the most recent WHO recommendations as a guide. But in addition today, we're going to discuss the challenges and opportunities for vaccine strain composition with the reduced public health threat from Influenza B/Yamagata lineage viruses.

The reason for this is two-fold. One is that, as you'll hear probably later in the day several times, there have been no B/Yamagata lineage viruses detected for over three years now. And our VRBPAC as previous meetings of this committee, as well as WHO experts at the most recent strain composition meeting have advocated for vaccine composition changes that include removal of the B/Yamagata component, as well as some consideration for other composition possibilities.

I want to spend the next two slides reminding you of what we've done recently and what's been recommended most recently. So, this committee last met in March, following the WHO recommendation for the Northern Hemisphere 2023-2024 season. In other words, the one we're in starting now. The WHO met on February 24th of this year our VRBPAC met a week and a half or so later. Once again to consider the antigenic composition for the 2023 2024 Influenza season. The committee met, discussed, made recommendations for Influenza A/H1N1, both for egg-based and cell and recombinant-based vaccines. Did the same for H3N2, also egg-based and cell and recombinant-based vaccines, vaccine recommendations, and the committee discussed Influenza B for trivalent and quadrivalent vaccines, recommending a B/Austria/1359417/2021-like virus. And finally, discussed the Influenza B for quadrivalent vaccines containing a B/Phuket virus.

Most recently, the WHO met about last week to make recommendations for the Southern Hemisphere 2024 season. In other words, next summer here in the Northern Hemisphere, next winter in the Southern Hemisphere. The recommendation was published on 9/29 last week. And in that recommendation, they recommended that trivalent egg-based vaccines for use in the southern hemispheres contain the following: An A/Victoria 4897/2022(H1N1)pdm09-like virus, an A/Thailand/8/2022(H3N2)-like virus, and a B/Austria/1359417/2021 (B/Victoria/lineage)-like viruses. In other words, there was one change here from the previous northern hemisphere and that was in the H3N2 recommendation. The committee recommended that the B/Yamagata lineage component of the quadrivalent Influenza vaccines remains unchanged from previous recommendations. And that was a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus. But after that recommendation, the WHO made another statement. The WHO Influenza Vaccine Composition Advisory Committee expressed the opinion that quote, inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted and that every effort should be made to exclude this component as soon as possible. And as you can imagine and see, that will be sort of the basis of some of our discussions today.

Okay, so today we will have both a discussion topic and voting questions. And you'll see these later in the day, but I'm going to flash them up now so that you can get a preview. The discussion topic for the committee, we're going to ask the committee to please discuss possible antigen composition of future seasonal Influenza vaccines. Specifically, the advantages and disadvantages of retaining the B/Yamagata lineage component in the quadrivalent Influenza vaccine. Also, we will ask you to discuss the timing for possible removal of the B/Yamagata lineage component from current quadrivalent formulation, as well as to discuss opportunities and challenges for alternative vaccine composition formulations and the data needed to support such

changes. Following what I anticipate to be a robust discussion, we will have voting questions, these are shown on the next slide.

We have three voting questions planned. The first one is does the committee recommend excluding the B/Yamagata lineage antigen component from quadrivalent Influenza vaccines as soon as possible? The second voting question will be for the composition of egg-based trivalent 2024 Southern Hemisphere formulations of Influenza vaccines. Does the committee recommend, and we're lumping all three of these together, since these were the egg vaccine recommendations from WHO, an inclusion of an A/Victoria/4897/2022 (H1N1)pdm09-like virus inclusion of an A/Thailand/8/2022 (H3N2)-like virus and the inclusion of a B/Austria/1359417/2021 (B/Victoria/lineage)-like virus? And the third question we will ask the committee is for quadrivalent 2024 Southern Hemisphere formulation of Influenza vaccines. Does the committee recommend the inclusion of a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus as the second Influenza strain in the vaccine?

That concludes the introduction, and I'm happy to take clarifying questions. But before I do, I want to make one quick comment about our next speaker, Dr. David Wentworth. As most of you on the committee know, Dr. Wentworth has been serving as the director of the WHO Collaborating Center in Atlanta for several years, and he's been making these presentations about flu vaccine composition at least since 2019. This will probably be his last VRBPAC presentation in that capacity because of his appointment recently as the Director of Coronavirus and Other Respiratory Viruses Division at CDC. So, on behalf of the FDA, and for me personally, I want to thank David for all of his contributions. David has done a remarkable job of taking an enormous amount of data that the WHO sifts through for over a week and condensing it into a form that is easily explainable to all of us in about an hour, and that's no small feat. And I think he's done a

great job over the years of doing that routinely and making all of this understandable for us. So, anyway I would like to thank him personally as well as from the FDA for all he's done for us. I know the committee will thank him as well when he gives his talk, but on behalf of the FDA I'd just like to say thank you David and now I'll take clarifying questions if there are any. Over.

Q & A

Dr. El Sahly: Yes. Thank you, Dr. Weir. Dr. Portnoy has a question. Dr. Portnoy, please unmute yourself and go on camera, please.

Dr. Portnoy: Great. Great. Thank you. I understand that we're going to be having these three voting questions, but the Yamagata strain has been a controversy for quite a while now. If the committee votes no, will there just simply not be a quadrivalent vaccine or will the placeholder anyway, given that there's probably not enough time to come up with a different virus? What happens if we vote no?

Dr. Weir: Actually, I probably can't give you a final answer today. Obviously, it's complex and as you will hear from the manufacturers, we're pretty far. They will probably tell you they're pretty far along into preparing for a Southern Hemisphere vaccine. But regardless, we will listen to what the committee says, and we will take that under advisement and try to formulate a plan that is both practical and useful for the Southern Hemisphere. But I do think it is important once again to get a sense of the committee of how they feel about this and especially what they think about timing. So, I can't give you a final answer today.

Dr. Portnoy: Okay, thank you.

Dr. El Sahly: Question from Dr. Bernstein.

Dr. Bernstein: Thank you. I just had a quick question. I was wondering the choice of words as soon as possible. Is there a sense of urgency here that suggests that we should include that in this question?

Dr. Weir: Okay, so I can partially answer that. The way we have worded the question for you is verbatim from the way the WHO put it in their statement. You're right. The words as soon as possible are somewhat open to interpretation, depending on whom you ask. That is part of the reason why, in our discussion, we have specifically asked you to weigh in on timing. So, yes, it is a little ambiguous, but that's the reason we worded it exactly the way the WHO did.

Dr. Bernstein: Thank you.

Dr. El Sahly: I see there are no additional questions for Dr. Weir. So, we will move to the next part of the agenda today whereby we will learn about the global influence of virus surveillance and characterization from Dr. David Wentworth, who no one asked us to vote whether he can be relieved from informing us on the on the flu surveillance each year. So, we want to thank him, and we will miss him quite a bit. Dr. David Wentworth is still currently the director of the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza and Director of Coronavirus and Other Respiratory Viruses Division CORVD, at the CDC. Dr. Wentworth.

Global Influenza Virus Surveillance and Characterization — Dr. David Wentworth

Dr. Wentworth: Thanks very much. Can you hear me okay?

Dr. El Sahly: Yes, we can.

Dr. Wentworth: Okay, great. Okay. Thanks very much. I'm going to dive in. We have quite a bit to cover, but I'll explain. I'll go fast through a few parts of it based on what Dr. Weir already described to you. So, the outline of the presentation today is one thing I haven't done in the past, just dive right into the all the deep molecular details and I thought about it a bit and think that

now that we have a public meeting. And there's a lot more lay people watching it, it's pretty unfair. So, I'm going to level set with a bit of overview on Influenza viruses and the vaccine engine selection process and then I'll dive into the WHO composition meeting real quickly and then the selected information supporting the WHO Vaccine Consultation Committee's recommendations on the viruses Jerry mentioned.

So, there's four different groups of influenza viruses that infect humans, and so they're very different viruses from each other, and they have very different antigenic properties, and that's why we have a quadrivalent or a trivalent vaccine. So, there's two species of alpha Influenza viruses, the H3N2 and H1N1pdm09. So, H3N2 came into our population in the pandemic in 1968 and has existed with us ever since. And then the H1N1 came in as its name implied in the pandemic in 2009 and has been co-circulating with H3N2 viruses. Then we had the B/Victoria and B/Yamagata viruses. These split from an original progenitor virus in the eighties and kept diverging away from each other. And they're in the beta influenza virus species. And as Dr. Weir mentioned, we haven't detected a B/Yamagata since March of 2020. The major antigens that we spend a lot of time talking about in this meeting, particularly the hemagglutinin, or HA, is the virus attachment protein and then antibodies induced against that protein neutralize virus infection. And they also kill virally infected cells through a process called antibody dependent cellular cytotoxicity. So, these antigenic sites that are highlighted in light blue here, those are targets where the most potent antibodies against the virus bind. And so, these are neutralizing epitopes. And so when we're immunizing folks with vaccines, we're trying to get a high level of antibodies into these neutralizing epitopes. It will be very potent. We always get polyclonal responses to other parts of the HA that can neutralize a virus by killing virally infected cells, for example, and also through other things like opsonization, etc. So, the

neuraminidase plays a complete opposite role to the hemagglutinin. So, the hemagglutinin binds to the cell surface, and the neuraminidase actually cleaves the cell receptor surface receptor that the virus binds to and allows the virus to exit infected cells. It plays other roles, but that's its major role. And so, antibodies against this protein block that activity or some subsets of them do. And antiviral drugs such as oseltamivir block or inhibit this protein.

The genome itself is 13.5 kilobases in length, so it's a rather small genome. It's eight segments of negative sense RNA, and so you can see actually each of the segments in this thin layer microscopy here done from Dr. Kawoka's lab. That enables reassortment during co-infections. And so, this is one thing in this virus, not too many human viruses have a segmented genome and can have this process. So, this gives a tremendous evolutionary power because you can get two different parental viruses to go in and there's a possibility of 256 genotypes that will come out of an infected cell. The viruses themselves survive at the edge of error catastrophe. So, with every round of replication of Influenza virus genome, the RDRP or RNA dependent RNA polymerase is error prone. And on average, it makes one nucleotide mistake for every 10,000 nucleotides copied. And so, some consider that a disadvantage for the virus because it's really close to the threshold of extinction. Really, there's very many defective viruses for every replication cycle. And by defective, I mean if an individual particle tried to enter a cell, it wouldn't be able to complete a replication cycle, but it has a lot of advantages with increased adaptability. Variants are rapidly selected upon any evolutionary pressure, and it's a real evolutionary benefit to evade host immunity. And that's in part why we're here today. They rapidly evolve, these viruses rapidly evolve. They require continuous comprehensive virus surveillance, and it necessitates frequent updates to the vaccine.

And to drive this point home a little bit, the influenza viruses exist as a population of minor variants. This is true even in an individual, and I borrowed this from a review by Esteban Domingo quite a long time ago, but I really think it gets the point across. With RNA viruses, particularly viruses like flu and HIV that make a lot of errors, you have a population of viruses, in the millions of viruses, that are infecting you and in your lungs and upper respiratory track, et cetera. And upon pressure, particularly immune pressure for influenza viruses, particularly neutralizing antibody pressure, you can select for populations that escape that immunity. And there may be different mutations that each have a way of escaping the population immunity. So, you get some relative size groupings of various groups of virus that share certain mutations and can escape. And so, that can happen intra-host, but it also happens when we're transmitting the virus from one person to another. When you're inhaling a virus, you may have a lot of antibodies to all of these populations and therefore you're just not infected. Or you may have antibodies to some subsets of the population and not others and then it can be infected by those and then that can be transmitted on the population scale to others. And this is how Influenza really moves very rapidly through our population and rapidly adapts to evade our immunity, induced by natural infections and vaccines.

So, what are the goals and key questions addressed for vaccine antigen recommendations. These are the kind of questions we're asking. So our goal is really to identify antigens that will elicit immunity against diverse or diverging viruses that will likely co-circulate in the future. These antigens, the ideal ones confer breadth of immunity to match multiple lineages of viruses and therefore reduce the risks because we know many viruses will co-circulate in the future. And one of the misnomers is that we're trying to match a strain that will circulate six months from now. And that's not really true anymore. We are not trying to match just one strain that will

circulate. We're trying to look for antigens that have breadth, and we're trying to match that with fitness forecasting of the various clades and subclades that are likely to co-circulate in the future. So, the goals of the committee really have changed over the years.

Some of the key questions for the three to four viruses targeted by the different vaccines are, are or were there significant epidemics and where? What are the genetic subclades? And we always spend quite a bit of time on that now that have emerged in our population. Are those new emerging variants spreading geographically? So, are we seeing them in different countries and in different continents around the world? Are emerging variants anti-genetically distinct from prior or contemporary viruses? And that's the one of the big questions for updating our vaccine. And what's the proportion of this new group and/or groups and what groups are likely to predominate in the future? And do the current vaccines induce antibodies in humans? So, this is where a lot of this we can do with genomics and animal models. And then we need to look at how well vaccines that we're using now induce antibodies that protect against the various viruses. And then finally, if a new vaccine antigen is warranted, does it elicit antibodies with breadth, which recognize multiple important lineages? So, does it confer breadth of protection?

And this is the data we use. Epidemiologic data, virus surveillance data, genomic characterization of the viruses, antigenic characterization of the viruses, post-vaccination, human serology studies, vaccine effectiveness data. There's a global consortium that shares data with us in interim ways. Preliminary data before it's published. Data integration and comparison among the WHO collaborating centers as well as other reference laboratories and the availability and characteristics of new vaccine antigens.

So, that does it for the intro on flu and what we're trying to do. As Jerry mentioned, we met last week, and this is really the vaccine consultation meeting for the Southern Hemisphere

2024. The foundation of it is continuous surveillance that's conducted by the Global Influenza Surveillance and Response System, or GISRS. And we need to thank all the WHO Collaborating Centers, the National Influenza Centers, the WHO Essential Regulatory Laboratories, that's what the ERL stands for. FDA is an example of one of those laboratories, WHO H5 reference laboratories, and they support the zoonotic work that we do to also make vaccine recommendations for pre-pandemic preparedness, and it's supported by more than 122 countries from around the world, 155 national influenza centers or so. The consultation meeting was held from the 25th to the 28th of December. It was a hybrid meeting. It was chaired by myself and Dr. Nicola Lewis from the Francis Crick Institute, pictured to the side of me there. 10 advisors, which are the directors of the WHOCCS and ERLs. And we have a disclosure of interest at the start of the meeting. There were 33 observers and participants and experts from WHO regional offices and headquarters.

And then we had a public meeting with the manufacturers on the 29th of September going through a lot of the data in the same way I'm going to go through it today, but in more detail on a couple of the viruses. So, as Dr. Weir mentioned, these are the recommendations that we're dealing with. I have a multicolored slide compared to his, just to point out a couple of things. For trivalent egg-based vaccines I won't walk you through the names. They're going to be on the voting questions, but it's an A/Victoria virus. The reason this is highlighted in light blue is because you considered this last spring, and it is the antigen that's in our vaccine this fall now that people are going to get now. And so, it was a recommendation for the Northern Hemisphere already. And we're moving it up to that for the Southern Hemisphere 2024. So, it's an update to the Southern Hemisphere, but it's the same as the Northern Hemisphere. And you've seen a lot of the data related to that decision already. Then there's the A/Thailand/8 or in the cell or more

competent vaccines, the A/Massachusetts/18 antigen, these recommendations are updated both for the Southern Hemisphere for 2024 and in comparison to our current vaccine that we're getting this fall for the fall and winter season. And then the B/Austria component has stayed the same in both instances. And then we make recommendations for every licensed vaccine. And so, there's licensed quadrivalent vaccines. And for that, even though there hasn't been any circulation of the B/Yamagata, there's no reason to change that recommendation from the B/Phuket/3073. We have no data that would indicate we need to update that. And I'll go through some of the rationale that Dr. Weir described about our statement, and this isn't a WHO statement, this is a statement from the Vaccine Consultation Committee about that it would be good to remove B/Yamagata component from quadrivalent vaccines.

So now, this is a good slide just to indicate that we really have global surveillance. And so, any green continent, country listed, territory listed is sharing Influenza viruses with WHO collaborating centers between this period of time. So, there's many other countries sharing. But these were isolated between this period of time. And so, it also has to do with where the activity was. But I will show you that individually later for each of the subtypes and lineages. This slide's comparing the Northern Hemisphere and Southern Hemisphere, the box area is the region of time that we're looking at viruses from. And so, you can see in the Northern hemisphere, we had a lot of H1N1, that's the light blue colors. The peak was more in April here. It was following the season, the real big season here, in the end of 2022 and beginning of 2023. Then we also had some B virus circulation as well, and it's continued at low levels. And still just continuing at very low levels. In the Southern Hemisphere, they had a pretty good season. This is now back to pretty much normal Influenza seasonal levels, and you can see during their normal seasonal timing, they had a lot of H1N1, again, the light blue. Some H3N2, which is in the kind of

turquoise and then the dark is on subtype, so proportionally it'd be about the same. And then the same thing with B viruses and all the B virus lineage viruses tested where B/Victoria, and I'll go into that later.

So, to tell you about the H1N1 viruses now. Here, we have these lines represent years from 2020 to 2023 and the number of H1N1 viruses detected by the GISRS system. And so, you can also just see when the seasonality is. And here in 2023, the red line we have beginning in week seven, we start to see a rapid increase in the number of H1N1 viruses and then a decline and a tail off as we move into weeks 34 and 35. This rapid dip down in 36 and 37 may be not accurate because there's always a backfill of data that would then make that maybe more flat. But either way, it's tailing off quite considerably as a normal season does. This slide shows you the activity by country reporting to the GISRS system. And it's based on the percent positive Influenza specimens that are detected. And so, the light-yellow colors are between 0.1 and five percent activity. And then as you get into the more intense orange colors, you increase to 10 to 20% activity, for example, or 20 to 30% activity. And so, you can see some countries in Asia, for example, China and other countries in Southeast Asia as well as some countries in Europe and some countries in South America had pretty strong activity and many countries had between the one to five percent type of activity happening.

As I said, I'm going to be brief. So, I'm combining quite a bit of the detailed data in an overarching data. Here we have the overall (H1N1) pdm09 HA phylogeography. We've talked about this. This is the phylogeny of hemagglutinin. So it's the evolutionary tree of the hemagglutinin molecule. This large high level 50,000-foot view was provided by Cambridge University, our colleagues, Sarah James and Dr. Derek Smith. What we've labeled on here is the current Southern Hemisphere recommendation, Sydney/5. It's in this group of viruses and, and

Wisconsin/67 in this group of viruses. So, this bar chart here to the right of the tree shows from 2021, 2022, and 2023. And each of the lines represent months of the year. And the color-coded tick marks represent which continents the virus has come from. And so, you can see how the virus is evolving and where the different clades are co-circulating. And so there's still some geographic kind of clustering of the clades, but you can see now a lot more admixture. For example, here, you're seeing viruses in this major 5a.2 clade, but they're in the subset, the 5a.2a.1, circulating in Europe, North America, South America, and a few tick marks here in Oceania, the pink colors for example. And then we've had a subsetting from the 5a.2as. This was a major break off this whole part of the tree. Those are the 5a.2as. And so, Sydney/5s, 5a.2a a virus. And so is Wisconsin/67. But a little bit of further evolution has happened in this group here and they're called the 5a.2a.1. So it's a rather a subclade of this 5a.2a and that's the Wisconsin/67 virus.

Now, when we look at these viruses using ferret antisera and then we take that data and convert it to a visual illustration called antigenic cartography, which is shown here, we can see how we can take a large set of data lots of tables of individual tests and display them here. Easy for the human eye to kind of look at all the different viruses and to give you a sense of how these cardiographs work each of these gray squares that I hope you can see here represent a two-fold difference between that virus and the homologous titer of a parental comparator virus. And so, if you're within, say, for example, eight-fold, so eight of these squares, then we consider them really antigenically quite closely related. And as you get farther away from that, you start to become more antigenically distinct, just that's our kind of cutoff lines for definitional purposes. And so, you can see all of these clusters of viruses or whether they're the old Wisconsin/588/2019 virus, that was the previous vaccine virus, or the Sydney/5 cell virus here,

these antigenically are very closely related using the model ferret antisera. And then the Wisconsin/67 virus is here again, very close. And this circle around everything is how the serum from the Wisconsin/67-like virus that represents the square here reacts with all the viruses circulating. And so, you can see by a ferret immune response against these various antigens. This vaccine virus covers all of these viruses that are circulating. And the viruses that circulated prior to that are represented by this A/Guangdong-Maonan/SWL/1536. So these are the 5a.1 viruses. They're way back up here in the evolutionary tree that I'm not showing anymore. But they show you how antigenically distinct the 5a.1 and 5a.2 viruses were from each other via ferret antisera. And so, this kind of data doesn't support updating between these various vaccines. And we've discussed that in the previous meeting. So why are we doing it? And this gives you the summary of that data in tabular form. All the tests done show that we see everything looks quite good. 99% of the tests are reacting in what we call well with viruses tested. So 99% of the viruses tested with antisera against Sydney/5 are reacting well and that's also true for the egg cultivar of Sydney/5, 98% reacting very well.

And this is where the post vaccination human serology becomes very important. So, here we're lucky because we even have our collaborating center in the Southern Hemisphere was able to get sera from the Southern Hemisphere vaccine which included an update the human serology data I showed you in the spring was using the older vaccine virus Wisconsin/588 and so we saw more reductions in that sera. If you recall, we saw a lot of reductions in this 5a.2 group of viruses and that helps support the update to the Wisconsin/67, which is in this 5a.2a.1. Now, we're looking at sera with the 5a.2a antigen, the Sydney/5 like antigen from pediatric populations from Australia, adult populations that were given flu cell backs, the cell-based vaccine, or an egg-based vaccine inactivated vaccine for quadrivalent in Australia as well as elderly greater than 65-

year-old individuals in Australia. And so, what you probably can't see, because you don't remember, but these viruses, many of them were in the orange. So, we're looking at this the statistical analysis of the data, looking at whether or not the vaccine might be considered inferior for antigens, whereas you get into the more dark orange colors.

So, you can see that this update to the 5a.2a really worked well against a lot of different variants that we've selected that were emerging and some of these in what we consider pretty important regions. This one was selected. It's a Washington/22-like virus. It's a very infrequent virus. Very few of these have been found, but we selected it because of the particular changes that it has, and it did have some reduced reactivity illustrating that the system works. However, this is not a virus we're super concerned about at the moment. Then we tested these 5a.2a.1representatives, the Wisconsin/67, that's the cell-based vaccine for this fall and winter season in the Northern Hemisphere, as well as Wisconsin/47, which is just like it, but it has one additional change that we're seeing in a lot of viruses. And what you can see is, even with the update to the 5a.2a, we're still seeing, while the geometric mean titers are pretty good for the most part some centers, like CBER and the NIID in Japan were having some reduced reactivity to these viruses. And collectively, that demonstrated that the changes in the site CA, which I didn't belabor in the presentation, but these are consistent in these 5a.2a.1 proteins, subtly change the antigenic properties and reduce human antibody recognition. Although the ferret antibody recognition still looks good. And so, this is a pretty subtle change between these two viruses but likely to further improve the vaccine.

With regard to the neuraminidase inhibitors, antiviral susceptibility for H1N1 viruses of over 5,000 viruses tested only 18 showed resistance in genetic or phenotypic analysis studies. And with the endonuclease inhibitors, such as biloxavir, marboxal, of over 1800 viruses tested,

only two showed suggestions of resistance in genetic or phenotypic analysis. So, to summarize the H1N1 taken together, the committee felt the data supported updating from the Southern Hemisphere 2023 vaccine antigen, which was a Sydney/5 clade 5a.2a for the Hemagglutinin to the same antigen recommended for the Northern hemisphere in 2324. The Wisconsin/67/2022-like HA clade, 5a.2a.1, which just has those, a couple, two amino acid differences between the two.

The H1N1 virus is circulated globally and predominated in most regions. A phylogenetics of the hemagglutinin genes from viruses collected in this period showed nearly all were 5a.2a. And so, that recommendation really was dead on with regards to what was circulating, or they were 5a.2a.1 and that predominated in North America, Central America, and South America. While ferret antisera didn't distinguish between the various 5a.2 clades, whether they were a 5a.2, like an older Wisconsin/588 from 2019, or a 5a.2a, like the Sydney/5 from 2021 or the 5a.2a.1 like the Wisconsin/67 from 2022. However, the post-vaccination human seras showed reductions in geometric mean titers associated with some of the substitutions in important antigenic sites, such as CA.

On the good news side, the interim vaccine effectiveness estimates from the Southern Hemisphere indicate that the vaccines were effective and it's consistent with the A/Sydney/5 being in the vaccine. Nearly all the viruses analyzed, showed susceptibility to the antivirals. Okay. We've got a hand raised. Dr. Offit.

Dr. El Sahly: Should we leave the questions till the end?

Dr. Wentworth: It's up to you. I'll do it either way.

Dr. El Sahly: Let go with that. Sorry, Paul.

Dr. Wentworth: Okay.

Dr. El Sahly: Let's do it that way. Thanks.

Dr. Wentworth: Okay, so now to turn our attention to H3N2. Again, you've seen this graph before. We're looking from 2020 to 2023. I'll focus on the 2023 period. Here, we have January coming down from the northern hemisphere season with a brief lull and then an increase in H3N2 viruses again beginning around week seven and eight and then peaking around weeks 10 and 11 and dropping from there. And again, this sharp decline, I wouldn't believe that. That's a data reporting issue. People are still reporting data from those timeframes. So, Influenza H3N2 activity globally, you saw this slide, I explained it before, again. Some of the regions where we had the bigger epidemics were in China and Norway, for example, in South Africa, and we saw some in Southeast Asia, Indonesia, other areas. But many areas had 0.1 to five percent circulation as well. So we have viruses from around the globe to analyze, but we are taking note of those locations that had higher levels of activity with regard to the overview of the H3N2 phylogeny. I've explained this tree before. So, this is a tree going back to 2021 and into the present. The viral evolution for the most part is kind of going down the tree.

The Darwin/6, the current vaccine virus antigen is shown, its approximate location within the tree is in this group here. The tree breaks up at two sites. We have this major clade one and major clade two. We've shortened the name from this long classification, if you've been following, these are the 3c.2a1b. Period 2a, period clade 2 that's this number here, or they were played one and we've seen basically clade 2 viruses circulating everywhere. These have continued to evolve and break up into the clade 2b and 2a, and within the 2a group we've had a lot of diversification happening and I won't walk you through each of these names, but we will talk about some of them as we go. One of the major groups currently circulating so you can see in the months in 2023 here being this emergence of this clade 2a.3a and the subgroup of that

2a.3.1, 3a.1, so that's these viruses here. And you can see how they were previously circulating maybe even initially in North America and Europe and then got into Asia and Oceania and also back into Europe. So, this is a little bit closer view of that tree. This is data produced by Dr. Kondor's group in the CDC and so it's showing you the major recent clade 2 subclades. These are the 2a.3a.1s, which I just mentioned. An example of that subclade is this Massachusetts/18 recommended for the vaccine and Thailand, so that's the cell-based and the Thailand/8, which is the egg-based vaccine. You can see their location in the tree here. That's why it's highlighted. It's in the top of the tree in this bar, that's blue represents the 2a.3a.1 clade. And then the other groups that have been predominant. We had a lot of these viruses circulating in our seasonal last year and even to a certain extent over the summer. The 2b viruses, these are towards the bottom of this tree here represented by the Florida/57 viruses, this yellow bar. And then the 2a.1b viruses represented by the A/Michigan/60/2022, which is right here and in this green bar here. So, all of these viruses are here.

Now, one thing I want to point out, and I've highlighted in light blue is the parallel evolution. So, this recurrent evolutionary change from multiple subclades within the tree from an isoleucine at position 140 to a lysine or a methionine, and the lysine is more frequently occurring. And so you can see that in the 2b viruses. A number of them now have this 140K substitution. You can also see that in the 2a.1b viruses, nearly all of them have the 140K substitution. And in the 2a.3a viruses where they have the I-140K substitution. This group here with the I-140M represented more by this Georgia/19 virus has declined since its emergence previously. Now, this is an integrated phylogeographic tree. So, the tips of the tree are colored by the region where the viruses were isolated, for example. And so, you can see the more recent H3N2 activity happening in Asia. You can see a lot of these viruses were isolated in that part of

the world, both in East Asia and China, for example, as well as in India with the more bright orange. So, you see some patching based on the geography still, and then some admixing here. You can see the multicolor of this group of viruses in North America and Asia and Europe, et cetera.

Now, if we go to the far right where these tick marks are, that's February 2023. So, this time frame that we're interested in all the way to August 2023 and of course we have reduced numbers to look at that time point for the same reason. Sometimes there's a drop-off in activity and there's a backfill that will happen there over the next months. But we have really strong data up into July, for example. And so, you can see where these guys have been circulating and based on the tick marks and a little bit of a movement of the viruses. But in Oceania, these light pink viruses, for example, light pink dashes and in India and in China, we're seeing a lot of these 2a viruses, whereas the 2b we've seen more in Europe previously. And now we're starting to see some of those in India and China and Oceania. And then the 2b viruses down here, again, similar pattern with more of those in South America and Brazil, for example.

The final piece of this tree that I want to show you is the reactivity pattern of ferret antisera. So, ferret antisera are produced with the Darwin/6/2021 cell-like recommendation against various representatives from across this phylogeny. So, we look for viruses that are representative of the base of that phylogeny, as well as some of the odd viruses that have unique amino acid changes within that particular subcluster. And we select those for antigenic analysis, and that's detailed here in these two columns with less than eight-fold reductions shown on the left-hand column and then color-coded by whether or not they were less than four-fold or between four and eight-fold. Or then if they were greater than eight-fold into 16 and 32, they're

going to be in the next column over. So, the older clade, the 1a, the clade 1, it's sub-grouped into this 1a.1 virus. You can see that clade isn't reacting well with the ferret antisera to the Darwin/6.

But if you cast your eye up this column, you can see that most of the antisera is showing good reactivity across all of these viruses with some reduction, seen more in the 2b viruses than in most of the other viruses along the phylogeny in a little bit of a reduction in one of the 2a.3 viruses there. So, that's a way to integrate the antigenic data that I'm going to show you next on top of the phylogenetic evolution of the hemagglutinin, this shows you where the clades that I just described were circulating. And again, the primary clades circulating were these 2a.3a.1s and the 2bs, for example, with a little fewer of the 2a.1b. And so, you can see there are geographic differences between what's circulating in Europe and North America. We had more of the 2b and the 2a.1b viruses. Whereas in Asia, they had more of the 2a.3a.1 viruses, and this includes Oceania as well. And then you can see in South Africa where they had a high Influenza B epidemic, they had primarily 2a.3a.1 viruses circulating, for example.

To give you an idea how this has changed from the previous vaccine selection period until now, this is an estimated global infections of H3N2 HA clades based on sequence data that is pulled down from the shared sequence databases that we all contribute to in near real time. And then estimated to reduce the impact of sequencing bias. So, different countries and different regions around the world produced different amounts of sequencing data. For example, in North America and Europe there's a lot of sequencing data produced per infection versus in other areas of the world. So, to try to reduce that bias, we're multiplying the sequence data by the regional population size assuming a 10% infection rate and that's to try to level the playing field so that you can see real increases or decreases. And so, you can see we had all these different clades co-circulating, and again, the major clades were 2b, 2a.3a.1 and 2a.3a. And what we've seen in the

more recent timeframe, and this is shown at like about the 50 million bar mark is here is a real change with a decrease in the 2a.3a, a strong increase in the 2a.3a.1s, whereas the 2b have held fairly steady.

We also look at both the hemagglutinin and neuraminidase genetics, and we also look a little bit at the neuraminidase antigenicity, particularly for H3 viruses. Here, I'm showing you their phylogenies, but together so that you can see, remember, influenza viruses can reassort. And so, you can see how these two different genes are working together and in the evolution of the virus. And so, on the left, I have a hemagglutinin, you haven't seen something like this before, I don't think, but we call this a tanglegram, on the left you have the HA for the H3N2 viruses over the past two years, and the tips are colored by something called local branching index or LBI. And that's a measure of the evolutionary rate of the different viruses. So, it's one of the fitness forecasting measures that's used to look for viruses that may have increased evolutionary fitness compared to other clades. And I've pointed out on here where the 5a.2a.1, the base of these 5a.2a viruses sit. This is one of the reasons Darwin/6 has been such a good vaccine candidate is it really sits close to this whole group of viruses here that are circulating as well as these 2b viruses circulating. And here's the Darwin/9.

And so, the light colors suggest low levels of local branching index, and as you get into the warmer colors, you get higher levels of local branching index. So, what you can see on the hemagglutinin side is that the 2a.3a.1s have the highest LBI. And then when we look at the NA, now we're going towards 2023 from the right to the left, you can see that's also true for the NAs. Those viruses that are paired or correlated with the HAs from the 2a.3a.1, those NA genes and those viruses tend to be associated here and are also have higher local branching index. So it

appears these two genes have to work together. One binds, the other releases, and so they do co-evolve. And the NA often trails the hemagglutinin a little bit.

So, here's showing you the changes of the key serology antigens that we tested and really the difference between the Darwin/6 cell-based vaccine antigen and the Massachusetts/18 cell-based vaccine antigen. And I'm showing you here with no amino acid substitutions at Darwin/6, there's a lot of them compared to previous viruses, but I'm showing you as a blank slate. It's color-coded by the major antigenic epitopes, antigenic sites on the hemagglutinin. So, this peach color is antigenic site B, the green color is antigenic site A. A light blue color, antigenic site D. And the yellow color, antigenic site E. And then the dark kind of purplish-blue, antigenic site C. The receptor binding pocket, binding site is circled here, so it kind of sits in a pocket between antigenic site A and B. And these antigenic sites generate the neutralizing antibodies that have the most potency against the virus. So they really are good at blocking the virus receptor interaction and therefore blocking entry of the virus into a cell. So, the virus can't even get into a cell to start replicating and that's why they're so potent. With the Massachusetts/18, we have this I-140K that I highlighted in the tree that's been evolving in multiple clades. The 2b virus is having it, the 2a.3a virus is having it, and the 2a.3a.1s, which are increasing in proportion of having it. And then they also have this N96S, so the asparagine to a serine at 96. The reason this is starred is it introduces a potential glycosylation site at asparagine on number 94, so amino acid 94. It would be right over here. So, you can see both of these are really closely located to each other. The140K is in site A and the N96S is closer to site E, but either way, they're in important antigenic sites. We have some other substitutions. We consider these have been around for quite a bit in different branches of the tree and maybe kind of minor. When we rotate this molecule 180

degrees, you can better see this I-192F, so an isoleucine to a phenylalanine, that's a rather big amino acid change, right in the top of antigenic site B.

So, that's what's been evolving. And then when we look at antisera, as I already alluded to in our overlaid phylogeography that also included antigenic information. The CDC, we were seeing really good reactivity with antisera to the Darwin/6-like viruses with all the viruses we had to look at across the phylogeny. So, 100% of our viruses were reacting very well with this Darwin/6 cell-like antigen. So, a little reduction with the Darwin egg, but if we go down to, for example, the Chinese National Influenza Center, a collaborating center in China, you can see they had a lot of viruses to look at. And a lot of these were these 2a.3a.1 viruses, and they had a pretty considerable reduction in the number of viruses that were considered reacting very well with the current vaccine and had some that were reduced to the current vaccine. This was also a little bit evident with the VIDRL in China, or I mean in Australia. Sorry, that's our Australian collaborating center. Whereas the CRIC and the CDC, so the UK and the US had a pretty similar reactivity patterns. Again, we see a very similar pattern with the egg. We often see a little bit of a reduction with reactivity of egg antigens, particularly in the H3 viruses, so that is not surprising.

Now, this shows you one detailed hemagglutination inhibition test done by our colleagues at VIDRAL, and it's showing you a previous vaccine antigen, the Cambodia/EO823660 had a homologous titer of 640. And so, what we're really doing is comparing that homologous titer with the viruses that we're testing. And so, you can see there's a huge difference. More than eight-fold difference between Darwin/6 and this Cambodia, and you can see if we hadn't updated to Darwin/6, this wouldn't be reacting very well with any of the viruses that are co-circulating in this time frame here. You can see viruses from Sydney, Auckland, Singapore. A lot of Australian viruses from that collaborating center, Philippines. The color coding here is showing eight-fold

in the orange and greater than eight-fold in the reds, whereas the Darwin/6 here and the Darwin/9 egg are reacting well to 1280 homologous titer 640, only two-fold and then 320 four-fold. So, you get these color coding here with the light colors, but really the cell engine reacting still pretty well to most of these viruses. We are starting to see some reductions with some of these 2a.3a.1 viruses. Their clade is listed over here with the Darwin egg candidate. And then, if we look at this Thailand/8 cell, which really matches the Massachusetts cell recommendation or the Thailand/8 egg virus. We're seeing better reactivity with all the viruses that are co-circulating with the exception of this Brisbane/273 down there at the bottom here, which is the 2a.1b clade that we haven't seen expansion of, and rather a little bit of a contraction of that clade.

So we can take all that data, multiple HI tests like that, and I already showed you cartography before, and layer them into antigenic cartography. At CDC, we do something called High Contrast Imaging Neutralization Test, or HINT. This is a very granular assay. It's a little more sensitive than hemagglutination inhibition and it's pretty similar to this fluorescent reduction assay. So, this is also a cell-based neutralization assay done by VIDRAL, a CC at Melbourne. But what we're beginning to see is, while these are antigenic-related viruses, their clades are listed here and color-coded here. Again, the major clades being this 2b in the brown. Then 2b with a particular change that we've been watching. There's very few of these viruses around, but we tested quite a few of them. T135A in this light blue and then the 2a.3a.1, which are this green color in here. And then the 2a.1b are the more brown colors. And just to try to be a little bit briefer here, what we're seeing is there's a little bit of segregation and grouping between each of these now clusters. They used to be a little more admixed. The gray dots, I should have mentioned, are older viruses that were tested outside of this period. So, you can still see these are energetically very related with the ferret antisera, which works well again for energetic

relationships of H3N2 viruses. But they're starting to kind of diverge and spread apart and form their own small clusters. They still are very different than the previously circulating viruses that were the previous vaccine set.

And so here, we're showing you this, this data from Melbourne, different people doing the similar assay with different viral antigens and some of the same antisera. And so, you can see that the Darwin/6 cell and egg pairs are here. And where they sit, and they saw a lot of these 2a.3a.1 viruses in the green and that the Thailand cell and egg are well positioned to cover those. If we add the serum circles, so this is now looking at antisera, this is done from the CC in Melbourne, against the Thailand/8 cell. You can see how that sera now covers all these new earth 2a.3a.1s a little better than the Darwin/6 would have but it's going to lose some of these older viruses in particularly like the 2b and so this becomes the challenge. You have a one that's a little bit more broadly cross reacting, but the phylogeny and the evolution of the virus is moving towards these 2a.3a.1 viruses. And then again, this is showing you the Darwin/6 serum circle and how many of these are the Darwin/9 egg serum circle and how many of these 2a.3a.1s are no longer being covered and even some of the 2bs are being covered as well.

Okay, now let me tell you about the human serology. This is showing you the individual human sera analysis. I'll also show you a compilation next, but sometimes it's helpful to see this individual serum analysis. I'm only showing you the adult panel from Australia at the moment, just to get the points across, that the size of the circles that you're seeing kind of listed in the column go from one serum tested to 25 with the largest circle, and so that gives you a bit of a key. And this is looking at their pre-vaccination sera. So, we collect sera prior to their vaccination. And then their post-vaccination sera on the right in the orange. So pre is blue, and post is orange. And here we're looking at the Darwin/6. So, it's the kind of the homologous

antigen to what was in their vaccine. It's not the exact antigen that was in their vaccine because it may be Darwin/6 in the flu cell vax and Darwin/9 derived or similar in the egg-based vaccine the IV4 quadrivalent. Flu cell vax is also quadrivalent, I should mention that. Anyway, you can see the geometric mean titer, which is where this gray bar is, we have listed as 11 and it bumps up to 205. And then the 24% is describing how many in this group had a titer greater than or equal to 40 prior to vaccination. So, 24% had a titer. This is greater than or equal to 40 and 40 is a correlative protection for Influenza from Influenza viruses. And so, after vaccination, you can see we got a GMT of 205 with 88% now having a titer greater than 40. And then, now we look into the forward evolution of the viruses, looking at specific serology antigens based on the clades. So, the 2a.1b, Michigan/60, the 2a.3, which had these huge number of changes. So, a very rare virus, but we wanted to know if this one has evolutionary potential. This Georgia/19, the 2a.3a.1, the base of that group, Massachusetts/18. A number of them, I didn't mention this when I was talking about the evolution of the 2a.3a.1, but a number of them are evolving this substitution asparagine 122 to aspartic acid, which results in the loss of the glycan. And so that's represented by the New York/66. And then Florida/57 is the base of this 2b group. And we saw some of them having this change at 135, which impacts a potential glycosylation site. These have bigger impacts than just a single amino acid change. That's why we look at them. And then the I-142M representative, which I didn't think was going to be too big of a problem. So, what you can see is we have good reactivity against the 2a.1b. We still have 147 geometric mean tighter with 92% above 40. And then we saw a good reduction here by this virus, this Georgia/19. So, these mutations are definitely impacting our reactivity. Human serology reactivity when they're immunized with the Darwin/6.

The 2a.3a.1, on the other hand, we actually see pretty good neutralization of this group still. 205 to 194 and N122D even was neutralized pretty well. And as we saw a little bit more reductions with the clade 2b viruses, which circulated already in our hemisphere previously and are at the moment, flatlined, but I think on the decline. But, we actually had pretty good VE in our system, and we had a lot of these viruses. So they had geometric mean titers in the A160, 121, 189. Alright, basically a similar pattern. I have it on here just so you can see with the egg-based vaccine we have very similar pattern reductions in this group. Pretty good neutralizations of the 2a.3a.1 representatives and subtle reductions in the 2bs.

This is now compiling that same kind of data from all the groups, both WHO Collaborative Centers and Essential Regulatory Laboratories that do analysis of the post-vaccination human sera. Again, it's color-coded based on the likelihood or potential. It could be a possibly inferior vaccine to antigens that would be in the brighter orange colors. And here we're looking at a larger number of serum panels from the pediatric. Now, this is from the Northern Hemisphere vaccine. These two top ones as well as this nine to 17-year-old group. And then the adult, and this is from the Southern Hemisphere vaccines. This batch here all the way down. And so, kind of the top part of the graph is Northern Hemisphere vaccines. We're one of the few groups that did the testing there just to look at what the virus is, how they're doing compared to Northern Hemisphere vaccine and then the Southern Hemisphere down here. And so, as you can see from those bubble plots, the 2a.1b representatives, these Michigan/60, they actually had some of the lowest reactivity patterns and this 2a.3 with all these substitutions really across multiple centers. We saw that.

But in the 2a.3a.1, overall pretty good. But some CBER centers are seeing some reductions there and MHRA in the UK, seeing some reductions in some of the serum panels in

the 2a.3a.1s. We also saw some reductions in the 2b. So, I bulleted here just to bring the points home. The most significant reductions in the geometric mean titer or GMTs were observed in these 2a.1b, the 2a.3, and the 2b representatives. And there were fewer and more subtle reductions in this 2a.3a.1 clade viruses. With regard to the antiviral susceptibility, we're in really good shape. None of the over 2000 viruses were showing any resistance to the neuraminidase inhibitors and of the over 1000 tested with the PA inhibitors, the endonuclease inhibitors, 10 showed genetic or phenotypic evidence of reduced susceptibility. So, to summarize the H3, I know that was a lot of data, collectively, the committee felt the data indicated that updating the vaccines to the Thailand/8/AH3N2/2022-like viruses for egg-based vaccines, or Massachusetts/18-like viruses for the cell and recombinant-based vaccines for the Southern Hemisphere was warranted. The H3N2 subtype predominated in some countries in areas and territories. Most H3N2 activity was observed in southern Africa and in Asia. Phylogenetic analysis of the HA genes from virus in this period showed continued diversification of the clade 2a viruses. Their complete classification for those of you tracking is there. And whereas the 2b viruses have been more evolutionarily stable, but still circulate.

The major clades circulating in this period now are 2a.3a.1 greater than the 2b greater than the 2a.1b. The clade 2a.3a.1 increased in proportion during this period and predominated where H3N2 activity and epidemics occurred. The ferret antisera to the Darwin/6, it recognized viruses expressing most of the HA clade to derivatives. So, we're still seeing a pretty good reactivity. That's a very good vaccine antigen with limited reductions seen among viruses expressing the 2b and 2a.1, 2a.3a.1 HA clades. And it was more pronounced with the Darwin egg antisera. The Massachusetts/18 cell or Thailand/8 egg-like antigens reacted well. So, when they were given as antigens to ferrets, that sera reacted well with most circulating viruses, particularly

those expressing 2a.3a.1 HA clade genes. And then overall, most of the human post-vaccination sera, which they were vaccinated with Darwin/6-like viruses reacted well with most emerging lineages, including the 2a.3a.1. However, some recent HA clade 2a.1b., 2a.3a.1, and 2b virus representatives were significantly reduced in some serum panels in some other groups that were doing the testing. The interim VE from the Southern Hemisphere was very limited due to the low circulation overall. And then nearly all viruses analyzed showed reduced susceptibility to antivirals.

Okay, how are we doing on time? Getting late. So, I'm going to move through part of the Influenza B pretty rapidly. I wanted to be sure to cover the H3 very well and detailed. Again, this is the typical slide you've seen. Actually, in this period, we saw the increase of all three viruses around the same period of time. You can look at those here beginning a little bit earlier, in week four and tailing off by starting in week 16 or so. For the Influenza B viruses, this is where we saw activity. There was quite a bit of activity in the Americas, actually in South America and Brazil and in Mexico and North America and then in other parts of the world, Northern Africa and Europe we saw more activity.

When we look at the lineages circulating of those tested. 100% were B/Victoria lineage and 0% were B/Yamagata lineage. We had 22% in this surveillance system, this is provided by the WHO global Influenza program through their flu serve net, were not determined, but that's much better than the past. A lot of the national Influenza centers have been working hard to do lineage testing.

So, with regard to the Influenza B/Victoria viruses. I have to show you the phylogeny, but the good news is the majority of viruses circulating to date are all these V1A, 3a.2, I will call them 3a.2 viruses for short. These are the amino acids that they have differed from the

predecessor viruses or they're consistent among that clade and the B/Austria/1359417/2021 one sits kind of smack dab in the middle of that clade a little bit to the south there. And here's our serology antigens that we tested again across the phylogeny looking for differences that have specific amino acid changes in their clusters. Looking at ferret antisera to the B/Austria, it's reacting well with everything we tested in the 3a.2 groups and their subgroups. And we only see reductions against the older clade 3 viruses. So, they're the progenitor of these 3a.2 and they're represented by the Washington/2 virus that used to be in our vaccines, probably can't see it there. This is culminating of all the antigenic analysis, greater than 99% of the viruses are reacting very well with Anacera to the B/Austria cell-like virus and very similar for the egg candidate. So, not a lot of signals here to change the vaccine. The B/Victoria antigenic cartography, I've even overlaid the serum circles right away to save time, but you can see where the egg and cell, shaped like an egg, and cell shaped round and larger than their counterparts are circulating. I didn't point out on the tree, I will really quick, we have a lot of viruses with this 197E substitution. It's a pretty small change from an aspartic acid to a glutamic acid. And we wanted to understand whether or not that was making an antigenic impact. You can see the color coding here, the light green, the base, and the more olive color with the 197E add mixing and covered well by the antisera and that's also true. So, this is data from London and data from Melbourne.

Again, with the B human serology, the post vaccination human serum analysis with the big B/Victoria viruses, many different 3a.2 viruses were tested with different amino acid substitutions. All reacting very well with the post-vaccination human sera, and the 1a.3 viruses, which are older, represented by Washington/2. You can see a clear distinction now between these two. Although there still is some memory response, for example, as you get older, where they have a geometric mean titer of 135. The memory response is still boosting to 72 in this

Washington/2 group. So, that's always important to note. We don't see that in the young kids, of course. With the B/Victoria Lineage antiviral susceptibility. It's here over 2000, only six showed high evidence of highly reduced inhibition and five of these had this particular change K360E. We like to point those out for people that are really interested in inhibition or resistance to inhibitors and then of the endonuclease inhibitors of over 1,300 B/Victoria lineage viruses looked at in this period, zero showed evidence of reduced susceptibility.

So now, to the B/Yamagata. As Dr. Weir mentioned at the outset, there have been no confirmed detections of B/Yamagata circulating since after March of 2020. And this coincides with the COVID-19 pandemic. Of the over 15,000 Influenza B viruses collected between February 1st and August 31st, this timeframe that we're interested in, and lineage tested, no B/Yamagata lineage viruses were confirmed. Now, we periodically see from one of the National Influenza Centers or other places around the world, the potential detection of initially identified as a B/Yamagata lineage and so, these will pop up. Each of the collaborating centers that work with the various National Influenza Centers will reach out and get the viruses for secondary testing and confirmation. And so, of those 13 were confirmed to be B/Victoria lineage viruses or were just negative for Influenza B overall. And two were not available for confirmation. So, the specimen was all gone and did not yield a sequence data or virus isolate at the location they were originally identified in.

The absence of the confirmed detection of naturally occurring B/Yamagata lineage viruses is indicative of very low risk of infection by B/Yamagata lineage viruses in humans. It was our opinion as the WHO vaccine composition advisory committee, that while both trivalent and quadrivalent vaccines remain safe and effective, the inclusion of the B/Yamagata lineage antigen in quadrivalent Influenza vaccines is no longer warranted. And every effort should be

made to exclude this component as soon as I put in here, practically possible. And we can discuss that, but basically as soon as possible was meant to be, we know there's different cadences for different manufacturing processes. And the fact that the committee recognizes national and regional authorities are responsible for approving the composition and formulation of vaccines used in each country and should consider the use and relative benefits of trivalent and quadrivalent vaccines.

So, we understand that at number one, we're supposed to make recommendations for what's licensed. And so we make a recommendation for tri and quadrivalent vaccines. But we also wanted to make this point that we don't think at this point in time it's warranted. It's very difficult to determine if B/Yamagata lineage viruses are really extinct. And so as soon as possible is meant to say both what needs to happen for manufacturing and quality control and for approval in the regulatory authorities, this isn't something you do in one day.

So, Influenza B virus summary, the only Influenza B/Victoria was available for analysis. Collectively, there was not evidence that updating B/Vic vaccine antigen from B/Austria was needed. I think you could see that quite clearly, even though I went through it rather rapidly. The phylogenies of hemagglutinins show that they vastly predominate. They have global dissemination, so they're really fit viruses, but while they continue to diversify antigenic distinct viruses expressing the progenitor clade, 1a.3 and 3a.1 genes continue to decline. So, all these viruses were antigenically related, and that's shown in the next bullet. And post-vaccination human antisera analysis did really well against these viruses. Also, the interim vaccine effectiveness estimates from the Southern Hemisphere, which had quite a bit of Influenza B circulation, indicate that the vaccines were highly effective in this period. And nearly all the viruses analyzed showed susceptibility to antivirals.

And, as Dr. Weir mentioned at the outset, it's my last VRBPAC presentation. I want to thank you, the committee, for your intense deliberations, and for really being able to follow my hurried presentations that try to compile a week's worth of information into an hour. You follow it extremely well and ask really impressive questions to me. Dr. Kondor, who's been the Deputy Director of our WHO Collaborating Center for as long as I've been the Director, is now going to be serving as the Acting Director. And I want to introduce you to her. She is responsible for a lot of the beautiful phylogenetic analysis and data integration you see in these presentations. And with that, I have my disclaimer and I'll stop. Thank you.

Q & A

Dr. El Sahly: Through the forest, Dr. Wentworth, as always, walking us through a very complicated dataset with a lot of certainties and uncertainties. We have the first question from Dr. Offit. Please unmute and go ahead.

Dr. Offit: Yes, thank you. So, David, thank you for that very thorough presentation. I'm trying to understand this virus. So, when we talk about flu, what we talk about is the evolution of the hemagglutinin or neuraminidase away from antibody recognition. So, my question to you is, do T cells play any role in protection against this disease? Because presumably the T cell recognition sites, whether it's CD4, CD8 positive cells on these A proteins are, if it's true, similar to other viruses, are fairly well-conserved. So you would think that there wouldn't be the kind of strain-to-strain variation that we see with regard to antibody recognition. Do T cells play a role? Or said another way, if you had, let's say you just had a nuclear protein vaccine, which will have T cell recognition sites, would that in any way be effective in preventing this disease? Thank you.

Dr. Wentworth: Yeah. So T cells are important. I don't want the immunologist friends of mine to tell me that I'm bashing T cells, right? So they're critical. And, and even for antibody help. And, you know all this, Dr. Offit, you know just to get the right antibodies made, you need good T cell recognition in some ways. The issue with Influenza is its speed. So, as a negative strand virus, it's poised to replicate almost as soon as it un-codes inside the cell. And I don't want to get into the deep virology of it, but it carries all its replication machinery into the cell with it. So, within six hours of infecting a cell, it's already producing progeny virion. And within overnight, an individual is now basically having millions of viruses in their respiratory tract and they're obviously expanding logarithmically. And then, you're transmitting Influenza often before you even feel sick. And so, where the T cells become most important, particularly CD8 T cells, killing T cells, is clearing the infection. So, they are very important in clearing the infection, but if you think about the evolution of the virus, it's a lot and they do impact the evolution of the virus. I don't mean to say that they don't, but Influenza has really gone in done its damage and transmitted before T cells can really have a huge impact. Remember, they're going to take out virally infected cells and they may be resident in your respiratory airway at some level, but not at the level needed to really protect you. And so, the primary driver of Influenza evolution is the ability to escape those neutralizing antibodies, likely antibodies that are really IGA antibodies in the mucosal surface. Right? But, then it's come in, done its damage, and often transmitted to many other people. Now, the sooner T cells come in, they can actually reduce that transmission to other people in the later stages of infection. And so, there is evolution at T cell epitopes that we see. But, if I were to show you that on the same tree, I show you a hemagglutinin evolution against neutralizing antibodies. The time scale is so different. It's like a 10-year period and you

can start to see key epitopes in nucleoprotein, as you mentioned, start to have an evolution impacting them.

So, from my perspective, I think that is saying that they do matter. They clearly matter for clearance because folks that have immunodeficiencies with T cells have trouble clearing Influenza virus. And in that, the sooner you can clear the virus, the less likely you are to transmit it in the later stages of infection. And that's how it impacts the evolution of the virus. But when we focus on the thing that has the fastest impact on the virus is the neutralizing antibodies to the HA, then to the NA. So, when we focus the vaccine selection more on the HA, we're really picking the tip of the sphere of Influenza evolution. And so, by moving with that tip, you're often updating T cell epitopes unbeknownst to you.

Dr. Offit: So, thank you, David. Just one quick follow up question if you don't mind, Hana. So, if you look at, for example, work by Daniel Corey and others in Australia, as well as T cell immunologists here regarding SARS CoV 2 infection, it does look like CTOs do play a role in protection against serious disease and there is at least for SARS CoV 2 fairly conserved T cell recognition sites. So, are you saying that Influenza is different than the SARS CoV 2 in terms of its rapidity? Because my understanding regarding CTLs is that the virus enters the cell very quickly. The proteins are broken down and then these 8 to 15 more peptides are put on the surface in conjunction with class one glycoproteins in an hour. And then in theory, they kill me, I'm infected with this virus and then CTLs play a role. Are you saying that it's that those two viruses are different than in terms of how quickly CTLs can make a difference?

Dr. Wentworth: No, I think they're very similar from that perspective. And if you look at the evolution of SARS, it's actually kind of similar to flu SARS-2 with the mutations in the spike being really predominant, whereas nucleocapsid of SARS having very few changes. And again,

nucleocapsid would be highly targeted. The whole genome is highly targeted by T cells. So, I think it's the same story. If you were to say protect from serious disease, which is what you said for SARS, that's true for flu as well. You're protecting from serious disease. And what I was driving at is what's driving the evolution of the viruses aren't trying to cause serious disease, right? To anthropomorphize them a bit. They're trying to spread and make more of themselves. And so, the best way to do that is to get into another person and infect that other person. Right? And so, even for SARS, you're seeing the primary evolution happening in the spike at regions where neutralizing antibodies impact SARS.

Dr. Offit: But you're saying then that if I'm infected with the flu strain and then the following year, a different flu strain, that I am to some extent protected by against serious disease because of those cross-reactive CTL recognition sites.

Dr. Wentworth: Yes

Dr. Offit: Thank you. That answers my question.

Dr. Wentworth: That's what I'm saying.

Dr. Offit: I appreciate it.

Dr. Wentworth: But vaccination would also likely increase the resident CTLs in tissue resident CTLs in your respiratory tract. So, it offers still a benefit from a T cell perspective.

Dr. Offit: Thanks, David. And good luck in your future.

Dr. Wentworth: Thank you.

Dr. El Sahly: Thank you. Dr. Rubin.

Dr. Rubin: Thank you for that terrific presentation as always, and for all the presentations you've given. And congratulations, I think, on the new job.

Dr. Wentworth: Thanks.

Dr. Rubin: I have a question about B/Yamagata because you seem to be raising the question of whether or not it was truly extinct at the end. Can you do modeling to tell you how deep your sampling has to be in order to which you can give a confident threshold at which you can determine whether or not Yamagata is really gone?

Dr. Wentworth: Yeah, I mean, and this really gets outside of my area of expertise on the modeling piece, what you would need to do. What I will tell you is part of our thought process and discussions are you could try to do this. And so, for example, I think Rinderpest would be good if you really looked at how we determined Rinderpest was extinct, really good template for that. But it gets to a certain point of it's very hard to prove something's extinct. Right? And what we do know is that where we've seen B virus epidemics, we have not seen B/Yamagata, so it hasn't bubbled up to cause an epidemic. We would anticipate there would be outbreaks somewhere that really across the entire global Influenza surveillance system, the GISRS, that we might pick up an outbreak, particularly in, say for example, an elementary school, where people may not have had any exposure to B/Yamagata in the past, these children and so where it could potentially bubble up. And so, what we started to settle in on is what's the real risk of being infected? Not is it extinct? We can't know that right now. What's the real risk of being infected? And the real risk from our perspective is very low compared and that's the fact now. If it were to reemerge, then we can react to that. Right? But, standing around and really trying to do detailed studies to really prove something's extinct takes time. And that's the conundrum we have, I think. We have the likely potential that it is extinct versus acting now and doing more proactive things to further improve flu vaccine, open up antigen space for other viruses, for example, in flu vaccine. And we have the potential that it is extinct. And so, why should we be growing up large

quantities of virus manufacturing and using a vaccine that could potentially reintroduce something that's likely extinct? And so, I think that's what you have to weigh.

Dr. Rubin: Great, thank you.

Dr. Wentworth: You're welcome.

Dr. El Sahly: Dr. Shane.

Dr. Shane: Yes, thank you so much. And thank you, David, for a lovely presentation, this one and others. So appreciated.

Dr. Wentworth: You're welcome.

Dr. Shane: And I really enjoyed the introduction as well. My question actually relates to Dr. Rubin's, and I was just going to ask there was a percentage of B viruses that were not being able to be identified. Is there any concern that those might be Yamagata Influenza B or, or not? Thank you.

Dr. Wentworth: Yeah. So, I think we're always going to have that issue and our concern was quite minimal on there not being. So, to just better answer Dr. Rubin's question, one thing I do understand a little bit is trying to figure out what the level of predominance would be. And we actually have something called the rare event detection calculator on the website, it's part of our CDC calculations for how many viruses we want to survey, how much sequencing we want to do and all that. It's called Calculator B and it's on the American Public Health Laboratories website. But if you think about it, if we had done those extra viruses, so that would only push us from 15,000 to 20,000. And so, that's still not extensive enough to be super confident, right? That it's gone, right? So it's reducing your ability. So, for example, with that number, we know it's likely less than 0.05% of the viruses out there in that time window with 15,000 tested. Whereas, if we do another five, that's not going to really move that dial. We need to do an order of magnitude

more to get it to move one decimal place more, basically. And so, it becomes a very costly thing and a very time-consuming thing to try to do that. And you would still just be, well it's less than this probability.

Dr. Shane: Thank you.

Dr. El Sahly: I have a question and that's on your slides 34, 35, which sort of indicates that the Georgia strain is sort of the outlier in everything. Right?

Dr. Wentworth: Yeah, you're right. And so, we select these antigens for serologic analysis long before we have the sera. So, we're looking across the phylogeny, Dr. Kondor is very involved in this, and we're looking to the ones that really look like they have mutations in what we know are key antigenic epitopes and selecting those for analysis later. So, we have to grow them up, make sure they're highly pure, and sequences good and all that, so when the humans come, we can do the analysis. So, and they were these 2a.3 viruses represented by the Georgia/19, you've got a very good eye, they have changes in the hemagglutinin that are very significant.

Okay, so it's T-135K, so that removes a glycosylation site at position 133. And we know that can impact antigenicity I-140 K in the S-145N. So that also, that 145 position is really important in antigenicity. And so it was clear that we actually were starting to make potential candidate vaccine viruses out of that group as well and still continue to do that. But they were somewhat deprioritized as the evolution of the virus happened because, for some reason, although it's antigenically advanced in both ferret antisera and human antisera, it's not winning in the world of evolution of competition of Influenza viruses the way the 2a.3a.1s were. And so, it likely has some advantages of those changes, but there's likely some fitness loss, say, for example, in a non-immune post where it's not binding receptor as well. It's not as stable. You can

think of a million things, and we don't ever know why. But for whatever reason, it's not increasing. Nevertheless, it could be one that you're discussing six months from now when it gets an additional change either in the hemagglutinin or a change in the neuraminidase that compensates a little bit for that fitness loss. So, it likely evolved in a highly immune population and it's just not competing well in with all the other viruses in the population as a whole at this moment in time.

Dr. El Sahly: But the flip side of that is that the ones that were to the right of the screens, they are in the 3a, but not the Georgia. And they had reactivity with the Darwin, right?

Dr. Wentworth: Yeah, so, here's the crux of the difficulty that you have as a committee in selecting the antigens and we have as a committee in the larger global scale, clearly the evolution of these 3a.1s, we saw it last spring, but we weren't very worried about it because we still saw good reactivity with Darwin/6 ferret antisera for the most part. And Darwin/6 antisera was covering the breadth of that tree really well. And we didn't quite know yet because it was still not a large group of viruses, how well it would do in the evolution of Influenza viruses in our population. And what we've seen in this timeframe, and I showed you in that local branching index is really a rapid increase in this particular clade of viruses. And with our tools, we're not seeing much of a difference. And I can almost guarantee that the current vaccine we have for the Northern Hemisphere will do quite well against these viruses. But the question is, if these viruses that are continuing to expand and they basically have been in Asia where we have a lot of humans that live there and a lot of competition between viruses. If they continue to expand, which they're likely to do, and acquire some additional changes that give them a little bit more antigenic forward evolution compared to, say for example, Darwin/6, then having a vaccine in that group of viruses will be better. It will do much better. Even if these acquire two more

substitutions or something that would push them further away from Darwin/6. I really consider this update for the Southern Hemisphere not a major update, because we're staying right in that same clade of viruses. These are the most successful group. We have an antigen in Darwin/6 that we know is really a good antigen. It really creates good titer. We've known it's got good vaccine effectiveness for H3 viruses. And really what we're doing is keeping the same base number of amino acid substitutions that Darwin/6 has and adding that 140K, which we've seen in incident. Just one epitope that we've seen in multiple clades. So, even though it's a different clade of virus, say for example, the 2b with the 140K. One would anticipate that priming the human immune system with that 140K will do better against all those viruses with the 140K, for example. And then there's the other mutation that likely matters is that the 192. So really it's, in some ways, similar to the H1. It's not a huge antigenic difference between those two vaccines. But it's moving a little bit closer to the Influenza evolution. If you remember, Darwin/6 was a really great selection in a way because it was right during when the COVID pandemic was happening, we had very few viruses that were circulating to choose from. And that one really represented an antigenic group that looked to be expanding and created a breadth of immunity. And that's what it turned out to be. So, it's a little bit hard to move away from something you know is working good. But it's what I think you have to do with Influenza because it gets you closer. It brings you closer to the virus in its evolutionary activity.

Dr. El Sahly: Thank you. Dr Perlman.

Dr. Perlman: I just had two. So, great talk Dave. So, first, is surveillance at the same level as it's been in the past with all the political issues that have been occurring so that we have the same kind of reliable data?

And the second question is one, probably that people who've doing this for a long time can answer. If you go from three, four immunizations down to three, do you get a better immune response to the three remaining ones?

Dr. Wentworth: Yes, those are both really good questions. And so I think with regard to surveillance, even there's always some geopolitical issues happening in any, almost any Influenza timeframe that we're analyzing viruses because the system is fairly diverse, we get a lot of redundancy. So, I think we're in pretty good shape there. As I just mentioned at the end of the last question, it was actually much more challenging during the height of the COVID-19 pandemic when everybody was using a lot of pharmaceutical interventions and having to work on SARS itself. Not being able to do as much flu, but we just really didn't have a lot of flu circulation. And so, some of the countries that had it were able to get viruses to all the collaborating centers, et cetera. Here, now we're in pretty good shape. Probably some reduced amount of virus specimens from Eastern Europe, but a lot still sequence data from that region. And so, we can select specimens that represent those samples when we do our analyses.

And then to the second part of the question, I was not around when we moved from a trivalent to a quadrivalent. And I think it would be better for FDA to address that question. I think there's potential that if there's any immuno-dominance issues or things like that, that you may actually have a benefit, but I don't think we saw a lot of negative impacts of adding Yamagata in the first place.

Dr. Perlman: Thank you.

Dr. El Sahly: Dr. Janes.

Dr. Janes: Thank you. Dr. Wentworth, as we think about the composition for this year, and especially as we address some of the discussion points around. How to make decisions for

following years composition. I'm wondering has the group done calculations? There's, as you described, a lot of work done that's gone into selecting the panel of viruses that are tested and in particular I'm thinking of the ferret antisera data. A lot of work gone into selecting the panel of viruses that are tested. But I'm wondering about how those neutralization results could be integrated across the panel of viruses that are tested. In particular, would it be possible, or has it ever been done to calculate, let's say, the median neutralization titer across potentially circulating panel of viruses to inform and one could conceivably do that calculation? I would envision under different compositions of next year's vaccine to inform that decision. Or what would be the barriers to doing that calculation?

Dr. Wentworth: Yeah, so that's a wonderful question. And actually, we do that. So, we call it antigenic inference. So, if you can imagine a tree, maybe I'll share, I don't know. So, we do this now in partnership with Trevor Bedford and Richard Nair's group, both in Seattle, Washington and Basel, Switzerland. So, they are the codevelopers of a thing called Nextstrain. And you can yourself go to the Nextstrain site, pick seasonal Influenza, and not only see those types of trees that I showed you, but underpinning some of that is antigenic inference data coming from all the collaborating centers so that you can look at how antigenically distinct the various viruses are.

We also take the antisera to potential vaccine candidates and see how well we have different charts that we can use. It's just a little bit too much data to show you. And it gets very involved, especially online. But I think I gave the address for where I showed you the two trees and the local branching index in that same area. You can pick local branching index. You can pick antigenic advance and you can pick some things that underpin the antigenicity and so it will take two tested viruses and infer the evolution in between them to be about the same. So, it can't do much going forward, but if you have data against a group that now has 192F as an example,

and the base that didn't, you can kind of assume the things in between what is their antigenic profile. And so, we use a lot of that now and it's particularly useful in looking at potential vaccine antigens because we want one that looks to cross-protect against all of those groups better. And I think that might have been what you were driving at.

Dr. Janes: Great, thank you.

Dr. Wentworth: But we're trying to make everything as transparent and publicly available as possible. So, all of our sequence data ends up in near real time. As soon as we're confident that the data is correct, it gets into publicly accessible databases. And the easiest way for people to deal with it from my perspective is this Nextstrain, which takes that data and automatically makes trees and does a lot of these phylogenies for you. It can't do some of the detailed stuff that I showed you. But it does an awful lot.

Dr. El Sahly: Dr. Wentworth. You're staying with us during the discussion, right?

Dr. Wentworth: Yes.

Dr. El Sahly: So, Hank and Steve, would it be okay to ask your questions during the discussion to David? Because we're staying with the agenda.

Dr. Greenberg: Yes. No problem.

Dr. El Sahly: Thank you. I remember that you two are the first to ask questions during that time and we will break now. We have only seven minutes remaining for a break. So why don't we reconvene at 10:35?

Challenges and Opportunities for Vaccine Strain Composition with the Reduced Public Health Threat from Influenza B/Yamagata Lineage Viruses

Dr. El Sahly: Welcome back, everyone. In the next portion of our meeting, we will be hearing from industry representative regarding challenges and opportunities for vaccine strain

composition with the reduced public health threat from Influenza B/Yamagata lineage viruses. To go over this topic, we have Dr. David Greenberg, the Global Senior Expert Medical Strategy at Vaccines for Sanofi. Dr Greenberg.

Dr. Greenberg: Yes, thank you. These are Dr. Weir's slides. So, did you want Dr. Weir to go first or change the slides to mine?

Dr. El Sahly: You are on the agenda first. I think you should go first.

Comments from Manufacturers Representative — Dr. David Greenberg

Dr. Greenberg: While those are being pulled up, I'll thank you now for the opportunity to present the industry perspective during today's VRBPAC meeting. I am David Greenberg, Global Senior Expert, Medical Strategy at Sanofi. And the presentation I'm about to give was prepared in consultation with each of the other US licensed Influenza vaccine manufacturers. I'm an employee of Sanofi and my disclosure is shown here. Before getting into the content of the presentation. I'd like to comment that this is a fast-moving and complex issue. Following consultation with the other manufacturers, we submitted the industry slide deck to the FDA last week, and a great deal has occurred in the last six days, including the discussions and recommendations at the WHO Strains Selection Meeting on September 29th. We recognize that some of the industry slide content is already out of date and deserves update. So, I will do my best to provide that in my comments today.

I'll start by saying that we want to maintain and build public confidence and trust in Influenza vaccines. We value our partnership with public health authorities, regulators and the scientific community and other dedicated stakeholders to provide timely access to influenza vaccines and reduce the burden of disease worldwide. We hear and acknowledge the ongoing concerns regarding the B/Yamagata. Through this presentation, we are looking for cross-sector

partnership and an organized approach that preserves public health and confidence in Influenza vaccines. While it would be helpful to have scientific regulatory and implementation frameworks to help guide the proposed removal of B/Yamagata, we recognize we need to be agile and efficient in the transition. We are committed to work diligently with the FDA and other regulatory agencies worldwide. Please also understand that our interest in documenting the rationale and framework stem from our discussions with vaccine experts in the US and elsewhere, whereby they have challenged us to justify the rapid change. Some of the topics we should consider during the transition include the following, expectations for transparency around public health decisions to main confidence in the vaccination programs, acknowledging that QIV and TIV have similar reactogenicity and tolerability profiles. We do not want the public to misinterpret the removal of B/Yamagata is related somehow to the safety parameters, recognizing that the risk of B/Yamagata re-emergence from manufacturing sites or laboratories or LIV reassortment are hard to quantify. They're likely close to zero but because of robust safeguards that have existed for decades, and these risks may be lower than the re-emergence of residual undetected viral circulation or perhaps evolution of strain circulation during the post-COVID era. So, continued viral surveillance will be critical to monitor for re-emergence as we move forward.

We fully acknowledge several recent public statements by health authorities, of which only the first one is shown on this slide. At the end of the European Influenza Congress two weeks ago, Dr. Singh said the question is not if but when to remove B/Yamagata from seasonal vaccines and the transition should transpire in an organized approach. The second statement being the opinion of last Friday's meeting from WHO Vaccine Composition Advisory Committee that B/Yamagata in QIB is no longer warranted and every effort should be made to exclude the

component as soon as possible. And the third stems from Dr. David Wentworth's comments following the WHO meeting, I'm paraphrasing hopefully in an accurate way, that the transition is going to be different for different companies whether or not their TIV licenses were retained and whether their manufacturing process has changed. And he acknowledged the transition will take time. With all of this in mind, the purpose of our presentation today is to offer a timeline for this transition that best balances the desire to move quickly and with the commitment of ensuring uninterrupted supply and maintaining access and confidence in these important Influenza vaccines.

While we're aligned in executing the removal of B/Yamagata, we recognize that transition timelines will vary based on vaccine platform, manufacturer, and various global regulatory rules. Following the WHO/MHRA meeting on July 13th, the manufacturers responded to a questionnaire to determine realistic steps for successful global transition to TIV. And so, some of those data are shown here on the slide. There are 355 TIV licenses worldwide that need to be reactivated or submitted or resubmitted. 1,490 TIV variations needed to be updated with regulatory agencies globally. And health authorities in 174 countries will require new submissions to update manufacturing CMC and quality data to align with current quality standards. The time frame shown here estimates in the WHO regions based on historical standard regulatory practice. Up to 36 months in the Americas, Europe, Africa, and Western Pacific. Up to 48 months in Southeast Asia and Eastern Mediterranean. So, given our commitment to a successful transition, we look forward to receiving clear regulatory guidance and support from the FDA and agencies worldwide. We ask that the FDA provide leadership to this discussion globally and help reduce these timelines in the international markets and international regulatory

agencies. So, with this global view in mind, we now want to offer specific timelines for both Southern Hemisphere and Northern Hemisphere transitions.

So, I'd like to focus on the Southern Hemisphere first. We appreciate the critical role that VRBPAC has in recommending Influenza strains that the manufacturers will use in producing the Southern Hemisphere vaccines in shipment to those countries. Given the regulatory submissions noted in the previous slide, we asked VRBPAC to make a strain recommendation for both TIV and QIV during today's meeting, which will sustain global supply and avoid shortages. Timelines to obtain approval for the transition from QIV to TIV will vary among national regulatory agencies throughout the world. While TIV licenses are only inactivated in the US, in many countries, TIV licenses were either completely withdrawn or were never granted, thereby requiring manufacturers to submit new marketing applications that will need to be reviewed and approved. There are Southern Hemisphere countries that rely solely on CBER as the reference authority to release vaccine. That is, we cannot ship vaccine to some Southern Hemisphere countries without VRBPAC strain recommendation and FDA release. For Southern Hemispheric countries where QIV is licensed, but not TIV, we can only ship QIV. If VRBPAC does not recommend four strains, then manufacturers may not be able to supply those countries.

So, in summary, we asked for a PAC to recommend strains for both TIV and QIV formulations for the Southern Hemisphere 2024 season consistent with the recent actions of the WHO. While manufacturers work with dozens of NRAs On the required regulatory processes to execute the transition.

Now, let's shift to the US and Northern Hemisphere, that is, the next VRBPAC meeting in March. While we are committed to a successful transition, it's important to recognize that it will take some time. There is significant amount of regulatory work that will be required to transition

to TIV. Since we're unsure of the regulatory timelines, that is manufacturers have not yet met with CBER to discuss what is needed for their specific regulatory filings. There is a substantial risk to US supply if we're faced with distributing TIV alone just 9 to 12 months from now, that is the summer and fall of 2024. There are important manufacturing changes that have occurred since TIV was last distributed in the US. And these changes require dialogue between individual manufacturers and CBER. As of today, there's no clear regulatory framework for reactivation for each one of the manufacturers. Those discussions are yet to come. Based on our analysis and time frame that I'll show you in the next slide in a few minutes, we propose that CBER maintain QIV licenses through this VRBPAC meeting. And when you meet again in March, we will pursue activating TIV licenses in parallel, but allowing both vaccines to coexist through these two VRBPAC sessions would be prudent and avoid supply disruptions.

I'd like to illustrate the challenges with concrete examples. Since the time the TIV products were discontinued in the US and internationally, many changes have occurred in the Influenza vaccine manufacturing, infrastructure, quality, testing, container closure, packaging, or presentation of Influenza vaccines. And these changes have not been implemented with TIV. For some products and presentations, a TIV formulation was never licensed in the US. Manufacturing facilities across multiple companies and external partners were built and brought online for QIV, but TIV has never been manufactured in those facilities. End-to-end manufacturing, including quality and validation in many sites, are QIV specific and will need to be re-evaluated and dossiers submitted to regulators for TIV. Traditionally, it can take up to 18 months to generate new validation data and submit them to the agency to support licensure. So, clearly, we look forward to working with CBER to find a more rapid pathway for approval of TIV licenses wherever necessary. We should also note that when VRBPAC meets again, just five

months from now, to discuss the Northern Hemisphere 24-25 strain selection, most QIV orders will have already been placed by customers and manufacturing will be well underway. Therefore, we ask VRBPAC to select and recommend four strains today and in March to give the industry time to obtain regulatory approvals for TIV.

This diagram illustrates the vaccine manufacturing timeline for US supply for Northern Hemisphere next season. As a reminder, industry manufactures and distributes between 150 and 200 million doses of Influenza vaccine for private and public sector use in the US each season. As shown, the reality is that the process for the next ten Northern Hemisphere seasons is already underway if industry manufactures only three strains and then fills and packs TIV only. But full FDA approval for the new TIV formulation is not accomplished for each manufacturer by July 2024, then US supply may be compromised. We note that customers will submit their pre-orders for QIV in the next few months. So, the transition involves more than just manufacturing and regulatory approval. There's also substantial work to manage customers, which is a complex network of health care providers and health care systems. I've shared this diagram with you today to illustrate that the entire Northern Hemisphere supply, or significant portion of the supply, to be shipped next summer and fall could be lost if manufacturers produced TIV exclusively and some unpredictable circumstances were to prohibit obtaining final regulatory approval for TIV in time. I would like to underscore the complexity related to multiple different manufacturers in products, platforms, presentations that are necessary to fully supply the US health care provider and system. The significant number of unknowns that are across this complex environment requires us to keep QIV as an option for the next Northern Hemisphere campaign. In order for all of us to achieve our shared goal of providing an ample supply in a timely manner, allowing patients to be protected from the risk of Influenza.

Before wrapping up the presentation, I'd like to highlight that industry is open and interested in developing new QIV formulations to address the burden of Influenza and improve protection against currently circulating strains, thereby contributing to improve public health. Industry will collaborate with scientific experts, rely on surveillance globally. One option is to consider QIV formulations containing A3A strains. We'd like to collaborate with regulators to allow for some flexibility in QIV formulations based on unmet medical need. We will partner across multiple disciplines as shown on this slide. The potential to transition to QIV could be achieved in a timely manner if significant development is undertaken and partnering with regulators to align on requirements.

So, in conclusion, we are committed to maintain confidence in vaccines and enable a stable, predictable environment for influence of vaccine manufacturing supply and immunization campaigns. Acknowledging the current lack of public health threat from B/Yamagata circulation, we will work diligently to transition to TIV. We are dedicated to improving public health influence of vaccine confidence, vaccine supply and coverage rates in the US and globally. The transition to TIV will require close collaboration with CBER and many other regulatory agencies worldwide to reactivate or resubmit more than 300 TIV licenses, nearly 1500 variations and quality data to be updated in 174 countries. For the Southern Hemisphere 24, we request VRBPAC to recommend strains for both TIV and QIV formulations as we work diligently with regulatory agencies and health officials worldwide. Given that lead time required for seasonal Influenza vaccine manufacturing, contracting, distribution in the US, we request VRBPAC to recommend strains for both TIV and QIV only one more time after today. That's just five months from now at the March Strain Selection Meeting. And finally, we plan on exploring new QIV

formulations to improve protection against currently circulating strains by seeking collaboration with regulatory agencies and vaccine experts.

Thank you very much for your attention and I look forward to your questions and commentary during the discussion session. Over. Thank you.

Dr. El Sahly: Thank you, Dr. Greenberg. We will have time to ask him and Dr. Weir questions after Dr. Weir goes over his presentation. So, Dr. Weir, Director of the Division of Viral Products in the Office of Vaccine Research and Review at CBER, will give the FDA perspective on the challenges and opportunities for vaccine strain composition with the reduced public health threat from flu B/Yamagata. I would call it absent right now, but that's okay.

FDA Perspective — Dr. Jerry Weir

Dr. Weir: Okay, thank you. So, what I'm going to do in this presentation is briefly go back in time and review the development of quadrivalent vaccines and how we got there, not just from the historical perspective, but I think it's somewhat instructive as far as the issues that everyone wrestled with and particularly the types of data that we use to make that decision. So, I'll spend a little bit of time on that. Then I'll talk about recent developments and then go through a couple of slides each with challenges. You've already heard quite a few of these and some opportunities and then we'll open it up for discussion. So, if you go to the next slide.

Okay, this one's titled The Need for Quadrivalent Influenza Vaccines Containing Two B Strains. Beginning in 1978, trivalent influenza vaccines incorporated one influenza B and two influenza A (H1 and H3) components. Influenza B, though, diverged into two antigenically distinct lineages in the early 80s. And you can see a little diagram that I swiped from a Nature communication paper that shows the timelines for these subtypes of a influenza A as well as the divergence of influenza B. Influenza B was estimated, this was after the divergence into two sub-

lineages, was estimated to be responsible for about 26 percent of influenza infections in the years 1999 to 2012. During that time, though, the mismatch frequency between the recommended strain and the most commonly circulating influenza B strain was estimated to be about 50%. In other words, the recommendation sort of missed about half the time. I've thrown a couple of references for anyone that's interested. And so, discussions began, both the WHO, VRBPAC, other places around the world in the early 2000s, to discuss the feasibility and the benefit of adding a second B strain to the seasonal vaccine.

Okay, there were major issues that were discussed over this period of time, and these had to be addressed before there was a consensus on developing a quadrivalent vaccine. First of all, understanding the public health need and the value added by modifying the vaccine composition to cover both influenza B lineages. There was actually quite a bit of concern about whether 50 percent of the vaccine should be devoted to influenza B when it caused 25 percent of the disease burden. There was also the question of manufacturing capability and whether we were going to make a mistake of recommending a quadrivalent vaccine and then find out the capacity wasn't there to actually do this. So anyway, there were a lot of these issues. The VRBPAC started meeting and convening during the strain selection meetings to discuss the issue of two circulating strains; parallel discussions were taking place, WHO, other public health agencies. But as far back as 2007 the VRBPAC had a session on discussing the public health impact of two influenza B lineages. Some of the conclusions were listed at the bottom of this slide. B viruses were a major cause of epidemics every two to four years. They were prominent among children and young adults. The impact was less than that of H3N2, but probably either equal to or greater than sometimes H1N1 infections. There were manufacturing concerns related to different formulations, the capacity, there were some technical challenges, I'll mention this in just a

minute, and then, of course, even at the point in time of 2007, there was some question about what our regulatory options and how we would actually make this happen as far as having a second strain.

That was 2007. A couple of years later, the VRBPAC met and had further discussions about the utility of adding a second B strain to the influenza vaccine. At that VRBPAC, CDC presented an analysis that predicted a moderate public health benefit of including both B lineages in the seasonal vaccine as far as in terms of reduction cases of influence on hospitalization. The committee had further discussions at that time about the public health impact of the two circulating lineages and whether we should recommend influenza vaccines containing two B strains might be considered in the future. The committee was particularly interested in the possibility of this for the pediatric population, but the take home message from the meeting was that the committee encouraged all parties to collect more information to better understand the issue and to support regulatory decisions regarding inclusion of two B lineages in the seasonal vaccines. As you know, shortly after this meeting, there was a pandemic. But for the next several years, manufacturers worked with the FDA and other regulatory agencies as they develop candidate quadrivalent vaccines and conducted the clinical trials to generate supportive data for future vaccines that might contain two influenza B strains.

This actually talks about the actual licensure of quadrivalent vaccines and there was a VRBPAC meeting in February of 2012. At this point, this VRBPAC meeting was the first time that we actually made a recommendation for a second B strain. At the time, none of the manufacturers were licensed to make quadrivalent vaccines, but we wanted the recommendation to be made because we knew they were on the horizon, and they were close. And in fact, the committee asked representatives of every manufacturer to come to the microphone and report on

their progress and each of them came up and gave the status of their development. One admitted that they had already submitted a BLA to the FDA, although none were licensed. The committee was very enthusiastic at this VRBPAC. They expressed enthusiasm for a quadrivalent vaccine, and there were remarks that they hoped one or more would become available soon and sure enough, later that year, quadrivalent vaccines began to be licensed. I want to point out, and this is addresses one of the earlier questions from the committee today, approval of the quadrivalent vaccine was based on manufacturing and clinical data generated by each manufacturer that demonstrated safety, of course, but also the immunogenicity of the second B string component that was added as well as that the addition of that second B strain did not adversely affect the immune response to other vaccine components. So, that was the data package in summary that we use for the approval. All currently distributed seasonal influenza vaccines in the U. S. are quadrivalent basically one H1, one H3, a B/Vic and a B/Yam component.

I have a couple of comments about recent developments. As you've already heard several times today, there have been no confirmed detections of circulating B/Yamagata lineage viruses since March 2020, suggesting a greatly reduced public health threat and the possibility that these viruses are no longer circulating in the possibility. I do want to remind everybody that there is no animal reservoir for influenza B. In our previous VRBPAC meetings, committee members have discussed the recommendation for a B/Yamagata component for a quadrivalent influenza vaccine, considering the absence of detectable B/Yamagata viruses worldwide. At our last meeting on March 7th for the Northern Hemisphere recommendation, the VRBPAC made the usual recommendations on the selection of strains for the 2023-2024 Northern Hemisphere season, and as always, we were asked to vote on each vaccine component. Just to quickly summarize for the questions, one, two, and three, which were H1, H3, and B Victoria, the votes

were 13 yeses, zero no's, and zero abstains. For the fourth question, for the B/Yamagata component, the vote was seven yes, two no's and four abstains. To summarize the meeting minutes of that VRBPAC, the majority of the committee agreed with the WHO recommendation to continue to include a B/Yamagata component in quadrivalent vaccines for the Northern Hemisphere season, primarily because of the uncertainty as to whether a B/Yamagata virus lineage was truly extinct, that the consensus was that the issue would require further discussion at future VRBPAC influenza strain composition meetings.

So, this summer, the WHO organized a meeting. We had it on the 13th of July to discuss the issue of the influenza vaccine B/Yamagata component. We had a lot of participation from regulatory agencies, WHO, manufacturers, other interested-in-influenza-vaccine stakeholders. The meeting was held in conjunction with the 36th biannual meeting between the WHO Essential Regulatory Laboratories, the WHO Collaborating Centers, as well as the manufacturers. There has been a meeting summary written up. I don't think it's published yet. But just to summarize, there was general agreement at this meeting that in the absence of circulating B/Yamagata lineage viruses, that component of the vaccine should be removed. There was no agreement at this meeting about the timing of such action. There was a lot of discussion, but no agreement. There was concern expressed by manufacturers about the manufacturing and the regulatory issues that would need to be addressed. There was some concern expressed by some participants about the possibility of a B/Yamagata return. As you've already heard when the WHO convened the vaccine consultation meeting last week, they added this statement that we've already read out a couple of times. The absence of confirmed detection of naturally B/Yamagata lineage virus is indicative of a very low risk of infection by B/Yamagata lineage viruses. Therefore, it is the opinion of the WHO Influenza Vaccine Composition Advisory Committee

that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible.

Okay, so now I'm going to turn to a little bit of the challenges and opportunities. First of all, challenges for reverting from a quadrivalent vaccine, what we have now, H1, H3, a B/Vic, and a B/Yam component, to a trivalent with H1, H3, and a B/Vic. So, listed these as regulatory challenges. As you've already heard, and we acknowledge this, regulatory processes for reverting to a trivalent formulation differ in different parts of the world. That's true. In the U.S., all manufacturers of quadrivalent vaccines were originally licensed to produce trivalent vaccines, and these vaccines are still licensed even though they're currently discontinued. We do have processes in the U. S., procedures for removal of vaccines from the discontinued product list. You've also heard that there are manufacturing changes. Some manufacturing changes have been implemented for quadrivalent vaccines since the prior licensure of trivalent vaccines. We acknowledge that these changes that have been implemented for quadrivalent vaccines are specific for each manufacturer. So other words, some may have introduced new filling lines, new presentations, others may have made other changes. I will point out, though, that in the U. S, most of these manufacturing changes that are relevant to a trivalent formulation have already been reviewed as part of the quadrivalent license. Not all, but most. As I said earlier, there was some concern expressed in the July meeting about the re-emergence of the Yamagata viruses. I would point out that we do have a robust surveillance system and most of us, including the WHO collaborating centers, think that the system is adequate to monitor reemergence. And of course, the way to mitigate this risk or this worry is to retain quadrivalent licenses, and that would facilitate an appropriate vaccine response. And then finally, the challenge, the timing challenge. It is probably true that a global coordinated change in vaccine composition to a trivalent

formulation may be difficult to affect and this is for all the reasons listed above and that you heard in the previous presentation.

These are some of the challenges in changing the composition of influenza vaccines from the current quadrivalent composition to an alternative vaccine composition. So, the reason I'm mentioning this is because that every one of these meetings and every flu meeting you go to, there is always a lot of speculation that one could develop a different composition instead of the current one H1, one H3, one B/Vic and one B/Yam. So, I wanted to talk about some of the challenges here before I get to the opportunity. First of all, there is a challenge in developing a consensus regarding an alternative composition. We have seen and heard that there are several alternative composition possibilities, and these have been proposed. I'm going to mention some of these on the next slide. But the process for making our alternative composition recommendation has not been defined. There is also the challenge of generating the clinical data needed to support a particular alternative composition. This data would be required from each manufacturer, and the data would need would be needed for each alternative composition that was proposed. There are also technical challenges to a different composition. Some of the ones that are obvious, I've listed here, determining potency, determining identity, and then also determined to evaluate clinical outcomes, in other words, immunogenicity. All of these are challenges because of the close relatedness of some two different H3s, two different H1s, and some of these other combinations. One of the other challenges that we have to keep in mind is determining the effect of an alternative composition recommendation on vaccine timelines with our current H1, H3, B/Vic and B/Yam vaccines, manufacturers have a defined process, a time frame that they use, but they almost always prepare at least one of these antigens at risk before

strain selection decisions. So, I think before anyone makes changes to the composition, we would all have to ask ourselves whether there is any effect on the timelines that result from that.

Now I'm going to get into some of the opportunities. First of all, this just sort of states the obvious, I hope. The disease burden of influenza remains high. You can see I've put in a slide from the CDC website, and I think Dr. Wentworth mentioned this at the start of his talk. There's clearly plenty of ill, influenza, illness, hospitalization, and deaths every year. This hasn't changed. The other thing that hasn't changed is the burden presented by influenza B remains at about 25 percent of all the influenza cases in a season. And of course, all of us acknowledge that current vaccine effectiveness suggests that there is room for improvement. Again, if you just go to the CDC website, you can get vaccine effectiveness data for the last 10, 15 years. And I quickly looked at this and noted the adjusted vaccine effectiveness data ranges anywhere from 19 percent to 60 percent. So, there's clearly still room for improvement. And that I still think presents us with an opportunity to ask ourselves whether this is a chance to actually make a vaccine that is somewhat better.

Okay, so this is some of the other opportunities. As I said earlier, several different alternative compositions have been proposed. I listed one reference here that was a fairly recent publication that listed some of these. We had presentations at the WHO meeting in July, but you've also heard these over the years all sorts of proposals. Some of the ones that are most commonly proposed I've listed in the second bullet, for example, having two H3 antigens. Sometimes you hear proposals for two H1 antigens. But here the idea would be to better cover circulating virus diversity. There have been proposals for higher doses of H3 antigen. This would be to hopefully improve the effectiveness against the virus with the greatest public health impact. And then there have been the proposals for higher doses of all vaccine antigens to improve the

overall vaccine effectiveness. And here I just want to remind people that are experienced with high dose flu zone here with 60 micrograms of antigen as opposed to 15 micrograms in the standard dose. This results in the elderly with greatly improved antibody titers and improved effectiveness. So, there's reasons to support any of these compositions. The flexibility and composition recommendations would allow a timely response to virus diversity. These recommendations would have to be driven by public health need and by consensus. The technical considerations would have to be addressed. As I said, potency, identity clinical evaluation. It would be preferable to work on these technical considerations by collaborations between manufacturers and most likely the WHO Essential Regulatory Labs. And that was what was done for influenza B such that we could make an influenza vaccine with two influenza Bs. I remind you that every composition under consideration would be the supporting data from each manufacturer to update their license and our data needed for development for quadrivalent vaccines provides a general guide. In other words, immunogenicity of the new component, lack of interference with other vaccine components and safety. So, to summarize, the last two slides.

Development of quadrivalent influenza vaccines containing two influenza B antigens succeeded in eliminating mismatches between the vaccine component and the predominant circulating lineage of influenza B. Accumulating evidence indicates a greatly reduced and possibly nonexistent public health threat from the B/Yamagata lineage viruses. The absence of circulating B/Yamagata lineage viruses suggest that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted. Reverting to a trivalent influenza vaccine with H1, H3, and B/Vic components presents some hurdles which differ around the world but are probably manageable by coordinated efforts between industry stakeholders and regulatory agencies.

A change to an alternative influenza vaccine composition is an opportunity to provide flexibility and improvement for current vaccines. But this is going to require additional work, investment, and coordination among all stakeholders. It is, unfortunately, unlikely that removal of the B/Yamagata component from current quadrivalent vaccines can be coordinated with a change to an alternative composition. There's just a lot to be done. Global harmonization and standardization of any alternative influenza vaccine composition will require at a minimum: prioritization and consensus on the alternative composition to be considered; the generation of supportive data from each manufacturer to ensure the safety and effectiveness and new alternative compositions; and finally, and of course, the updating of licenses. I'll stop there. I think that's the last slide.

Q & A

Dr. El Sahly: Okay, thank you so much, Dr. Weir and Dr. Greenberg. I want to remind us that at 11:20 sharp, we need to be in the Open Public Hearing meeting, which has no one registered, but we still have to acknowledge right at 11:20 that this session is on and then we'll move on to the discussion. With that said, we probably have time for a couple of questions or maybe one question until 11:20 and I think Dr. Chatterjee was first to have a question. Dr. Chatterjee.

Dr. Chatterjee: Yes. Thank you Dr. El Sahly. I actually have several questions, but I will ask my first one now. So, this is for Dr. Greenberg. You mentioned that there are some countries where the trivalent formulations are not approved and that it would require approval by the FDA for those countries to then use the trivalent. So, in the absence of that approval, they are obligated to use quadrivalent. Did I understand that correctly?

Dr. Greenberg: Thanks for the question. The issue or topic is that for some Southern Hemisphere countries, they rely on release by the U.S. FDA of lot by lot, batch by batch. The vaccine that can

be shipped to those countries. So, although they may or may not have their own national regulatory agency, they rely on the U.S. FDA for release. So, we need to continue to work with FDA in the U.S. to be able to release, let's say, a quadrivalent to a country that does not accept trivalent yet.

Dr. Chatterjee: So, my question then was for other manufacturers outside of the U.S. do these countries have access to trivalent vaccines that might be shipped from other countries, for example?

Dr. Greenberg: I do not have that information. I'm sorry.

Dr. Chatterjee: Okay, thank you.

Dr. El Sahly: The 2nd question before the break is from Dr. Gans. Assuming it's a brief question.

Dr. Gans: I can reserve mine. Thank you.

Dr. El Sahly: Okay. Do you mind keeping your hand up? So, I know to call you after. Okay. I'll have a very quick question. Securus and Sanofi are the two companies for which we meet in the fall for the Southern Hemisphere in terms of FDA licensure. What is their share of the market in the Southern Hemisphere?

Dr. Greenberg: I can begin to address that. Our understanding that for the two manufacturers that you just named, there's approximately up to about 10 countries in Southern Hemisphere, where our companies ship and require the U.S. FDA release of those batches. And we're in the range of 10 million, maybe up to 20 million doses distributed to those countries. And I'd say most likely the majority of them are in Latin America.

Dr. El Sahly: And are y'all the sole supplier?

Dr. Greenberg: That I don't know, and in addressing that question in the previous one, I can't say for sure whether or not there might be other suppliers that could fill the gap. But you can imagine

there would be some disruption. I would say that there'd be a pretty high risk of lack of supply or supply disruption or timing of supply if they were to have to make arrangements with other sources.

Open Public Hearing

Dr. El Sahly: Right at 11:20. Thank you. So now we are in the Open Public Hearing session. There are no participants who have registered to be in the Open Public Hearing session, and hence we will be moving on to the next item on our agenda, which is the discussion.

Committee Discussion, Recommendations, and Voting

Dr. El Sahly: I think Dr. Gans is next and then we will move to Dr. Bernstein and Dr. Pergam. I did not forget about you. Dr. Gans.

Dr. Gans: Thank you so much. And thanks for all the wonderful conversation. I guess one of my major questions if we moved to over the process that has been outlined very clearly to remove Yamagata and we sort of keep open the quadrivalent. And I know, as Dr. Weir clearly said that these all need to be tested if we were going to move to a different formulation. I guess my real question is, because of the inflexibility in the process and how long it takes to really allow us to make these kinds of decisions, if we keep those, quote quadrivalents open and in the meantime, start testing some of the and as Hana had previously said, like, some of the other composition strains and clades that might be warranted is that something that we could potentially recommend at this meeting. And then my question is really if we were to change the composition because we're not worried about Yamagata and this is probably more for Dr. Wentworth, what would be the recommended changing composition? Are we worried about any of those H3N1s that we had sort of seen were maybe not as well covered and could that be a recommendation today?

Dr. Weir: This is Jerry, I'm not sure if that was for me or for Dr. Wentworth but I will chime in and say yes, you certainly can make that recommendation and in fact, that's the sort of thing that we're seeking some input from you. Again, I tried to stress that in my presentation that there are lots of possibilities out here, but there does need to be a little focus on some of them so that we don't have five, 10 different possibilities and something that's unmanageable. I think there does need to be some prioritization of what we think the biggest opportunity is, and then start generating the data to make that happen. That's just my opinion. I don't know if others have other comments about that. Over.

Dr. Gans: Yeah. And I think then for Dr. Wentworth since you spend the most time in that deep sort of blue world, what would be the recommendation if a composition change were to be considered for study?

Dr. Wentworth: Yeah. I'm going to give you a terrible non-answer. So, the issue is, we spent all our time looking at what we would recommend for the licensed vaccines. That's really our remit as the WHO Vaccine Consultation Advisory Committee And so that's the major thing. I'll give you an opinion now and it's my opinion, not the CDC's opinion, not the WHO's opinion, it would be very challenging. I think if you went there, my thought would be we would have to come have a delay for a little bit and come back with what would be the alternative? Like if you wanted to do an alternative strain, what it would it be? At this moment in time, it's a little tricky because it may be something like one of the two B viruses, so you'd pick a very antigenically distinct group. So, the more antigenically distinct group is the two B from the 2A, 3A.1s that was nominated. They're actually not that far apart. And so whether or not that would be that much of an improvement I think is the real question and why the studies are needed to compare just increasing the antigen all together versus picking two kind of divergent viruses. If it were up to

me to make the recommendation, I definitely wouldn't pick something old and something new, if it was just one vaccine for every age group and that's because of the immune boosting that you would get to the old thing would actually probably distract from the priming that you would get from the new antigen. And so those are the kinds of considerations that I think would have to be made. Now in a young population that's maybe never seen influenza H3 that could be very valuable, right? So, it's kind of giving them an older person's immune repertoire early in life. But this is really very theoretical. And so, what we work with is more like what exactly would be in this vaccine? If the committee really pushes to do something different, I think the solution from my perspective would be to say come back with a recommendation and then we could look at the serum with that in mind.

Dr. Gans: Thank you.

Dr. Wentworth: You're welcome.

Dr. El Sahly: I'm going to go back to Hank. Dr. Bernstein, please unmute.

Dr. Bernstein: Thank you. This question is for Dr. Wentworth. First of all, your presentations are incredibly enlightening, and I learned so much just listening to your comprehensive detail and in my mind, you will be missed. As Dr. Weir reminded us there was a mismatch 50 percent of the time between the B lineages included in the trivalent vaccine over a 10-year period, even longer with that lineage that's circulating in the communities. So, in your mind, what most supports the evolution of the virus during the 3-year period of the pandemic with SARS-CoV-2 co-circulating that's now reflective of what we can anticipate prospectively for future flu seasons. That part's not clear to me and I know Dr. Rubin asked a little about modeling as well.

Dr. Wentworth: Yeah. Thank you. And thank you very much for your remarks I really appreciate that. That's very kind. That's a really challenging question and I'll just precede it with

a little bit of history, and you've been on the committee quite a while and you'd know some of these things. I'll just recall them. So, prior to the pandemic, first right towards the end of 2018, beginning of 2019-ish, we had the emergence of in B/Victoria lineage viruses, what we called a double-deletion mutant. It was a deletion of amino acids, 162 and 163. And the vaccine that you all recommended, we recommended as a committee for the WHO was called A/Colorado (phonetic), I've forgotten the year. I think it was a 2019 isolate or it could have been 2018 but something around there. So that was an A/Colorado recommendation for that double-deletion variant because it had a big antigenic impact and really affected the viral antigenicity. And we did see a lot of those viruses cause a very early influenza B epidemic. And so, it was good vaccine, et cetera. Then very quickly after, within six to eight months, we had the emergence of a triple-deletion mutant. There was one triple-deletion mutant that almost emerged at the near similar time as the B/Colorado double-deletion, but that didn't seem to have a lot of what we call legs. It didn't have a lot of fitness and that kind of didn't go anywhere. But a second triple-deletion mutant emerged in the exact same site. So, it was 162, 163 and 164 were deleted and it also had a change at K 136. And that group was even more fit or did displace that double-deletion group, then about a six-month time frame. And again, we had a very early B/Victoria lineage season. And then the next season that would come up was Covid pandemic were all influenza contracted.

So, I think really part of the B/Yamagata demise is quite similar to how we have when we have a pandemic with human influenza, it will often displace the previously circulating virus. So, for example, H2N2 influenza displaced H1N1 influenza in 1957. We no longer saw H1N1. That had been circulating since 1918, very fit virus in humans, but even though it was very antigenically distinct, H2N2 coming in early and sweeping lots of people had a huge immune

response that could be both kind of non-specific, lots of innate immunity, et cetera, when the old virus is trying to replicate, as well as recall memory response to maybe non-neutralizing parts of the virus and a lot of t-cell responses to those viruses. So, my hypothesis really is that these two waves of distinct B/Victoria lineage even prior to the pandemic was heavily impacting Yamagata. We really didn't see any Yamagata then the pandemic happened. And again, we didn't see very many flu viruses and what came out of the bottleneck of the pandemic. We didn't see Yamagata again. So to look into what's going to happen in the future with the current B/Victoria viruses I do not know. Currently they seem to be, as I showed you in the tree, minor changes all along the hemagglutinin, but nothing really looking like it's being selected for, and so in one way that means that the virus is quite fit or quite happy in its current antigenic state and doesn't have a lot of pressure on it, whereas Yamagata apparently has a lot of pressure on that virus. I hope I answered your question, but that's a bit of a conjecture, a lot of conjecture about potential demise of the Yamagata because it really started before the pandemic even happened.

Dr. Bernstein: The SARS-CoV-2 sealed the deal.

Dr. Wentworth: Yeah, maybe. There are studies where even the two very different viruses can interfere with each other. But really, there was all the non-pharmaceutical-intervention-type things that we all did staying at home and masking and reduce travel and all of those things. So, I think B/Yamagata was under tremendous evolutionary pressure prior to the pandemic and the pandemic may have sealed the deal.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Pergam.

Dr. Pergam: Thank you. David, again, I would just I would say that one of the highlights of being on this committee is actually these talks that you get. They're fantastic. So, it's really a

pleasure to have you here and best of luck in the new position. I think we all agree that you're a tremendous asset to this committee for sure. I just was curious, and this is sort of an odd question, but I'm curious about the gaps in actual the data collection from the WHO. I still feel like there's areas of the world that are not really covered well. I mean, I look at the maps that you show, and an example would be Russia. We don't really have much in terms of viral sequences from those areas. Is there concern from the committee about areas where you're not getting enough data. I'm kind of following up on Dr. Perlman's question. I mean, obviously there's a lot of travel around the world and strains could be shared, but I'm always amazed at the sort of these micro-environments that are creating these new variants that are slightly different. So, I'm curious, is there any concern about gaps in the data that you guys have from areas where you're not getting quality data or limited data or not just Yamagata, but just in terms of decision making about this.

Dr. Wentworth: Yeah, thank you very much. And thanks for your comments. It's very kind. I think, yes, we always have concern about gaps, and this is one of the things. So, the WHO Global Influenza Program within the Pandemic Preparedness and Response kind of division. I've forgotten how they define it, which is headed by Wenqing Zhang, really does a lot of work in this space, looking at gap analysis. So where do we have gaps? How can we help? And so, part of it is building an infrastructure to turn the lights on where it's dark in a country that is maybe in an important area, the one thing I would say that gives me a little bit of confidence within the region's like, if you go a little bit higher than countries and get into WHO regions, these are sometimes called transmission zones. They're more regionally geographically oriented, but we do have good coverage within a region. Now, you've pointed out Russia, and this is one of the, to Dr. Perlman’s questions, usually we have a lot more sequence data from Russia and actually have

more viruses from Russia at the collaborating center at the CDC and the collaborating center at the Crick Institute in London, the Worldwide Influenza Collaborating Center there, so there's two national influenza centers in Russia and they're both working and collecting viruses and we are getting some sequence data out of those centers, but it's the shipping difficulties that have led to that in this period, the last couple of years it's shipping difficulties that have led to some problems there.

But overall, one of the goals is to identify those gaps and then try to support countries that are interested in doing flu surveillance and that they have to understand, it really has to be a country's decision if they have not a lot of influenza burden compared to their other diseases how much does it impact them? Do they even get vaccine? How much does it impact them? We have a lot of countries contributing that actually don't use influenza vaccine. So, it's not perfect. But I do think from a regional perspective, we're in pretty good shape because of the some of the things we can do. It could be improved tremendously by training. So, CDC and WHO And all the other collaborating centers work hard to train national influenza centers on detection. We provide reagents for detection in the hundreds per month. That kind of thing is supported at a global level, so it's not all led one country dependent that it has to be a huge investment to do at least Sentinel-type surveillance. But it can be improved for sure, but I think overall it's one of the best systems for the viruses just because it's been around for 70 years, and it was kind of the backbone for SARS coronavirus 2 surveillance during the parts of the pandemic.

Dr. El Sahly: Thank you. Archana had additional questions. Dr. Chatterjee.

Dr. Chatterjee: Yes. Thank you. So, I have two questions. I think these are both for Dr. Greenberg. One is with regard to the timeline. If I understood you correctly, David, you were talking about an 18 month or so timeline to be able to meet the requirements for trivalent

formulations that could be used across the world. I mean, I understand the manufacturing, the regulatory and the technical issues involved. One of the questions that I think could be asked is and recognizing that SARS-CoV-2 is a completely different virus, we're dealing with a pandemic, the resources that were deployed were completely different, but we were able to go from zero to having a vaccine within ten months that was deployable. The question may be asked is why is this process going to take this long? And could the timeline be shortened any at all? Dr. Greenberg:Sure. Thank you for the question. There's a couple of aspects. One is that we're already moving, we'll have these discussions with FDA soon and with the other national regulatory agencies. I don't think of it as 18 months in the sense that Southern Hemisphere of the vote is upon us today, in March is the Northern Hemisphere recommendations. So, in my mind, we're just talking about the next six months. Then of course, the manufacturers produce vaccine and distribute for that season, but that's really all that we're discussing. After that, I certainly hope that the discussions, particularly with the U. S. FDA, will move along swiftly and efficiently, and that we'll have then the go ahead for trivalent right after the next season. So, really our caution about the Northern Hemisphere season coming up in the March meeting is that there is so much work to be done between now and March that we're not sure if all of the regulatory steps can be completed and that there's so much confidence that all the manufacturers would have their approvals for trivalent in time to ship only trivalent in the next Northern Hemisphere season. Again, shipping started next July, August, September. We don't know. It's more of an unknown than it is anything else. And we have to move forward with our manufacturing and with the contracting and of course, working with the agency. So, we would honestly, we just want to be able to work with you and the agency to ensure that there's not a

supply disruption in case there's an obstacle that we just can't seem to figure out how to solve in time for the shipping next summer. So, that's really just the short-term concern.

Beyond that, we're planning to have TIV, and so that's our goal is to work directly with the agency and do that. And then for the other countries, we'll come back to you. We'll come back to you for the Southern Hemisphere '25 season. We hope that each of those countries where they rely on the U.S. FDA release, we hope that they've all given the manufacturers the ability to ship TIV. And if so, then then it's a good win for everyone. But we'll come back to you. Because again, those discussions haven't taken place yet. So, it's really just this meeting and a meeting in five months. And then we hope to be right on track with what the VRBPAC committee and the agency would like.

Dr. Chatterjee: I do have another question for Dr. Greenberg, but I can hold it until later.

Dr. El Sahly: Well, why don't you go ahead? It's fine.

Dr. Chatterjee: Oh, okay. So, this question is related to some of the comments we've heard, I think, from Dr. Weir and Dr. Wentworth with regard to alternative quadrivalent formulations. Could you tell us a little bit more about where the industry is at with working on obtaining the clinical data needed to support those formulations?

Dr. Greenberg: Well, the first step, of course, is as just discussed minutes ago about what is the right formulation and with what strains. So, none of us today have that answer. But we are very interested in in exploring those. And of course, it's going to depend from company to company, but those discussions then can take place with the agency. And each of those manufacturers, each of those companies can conduct clinical trials as they wish. So, I don't have an answer for you today, but I know that there is interest among generally the manufacturing community to move in that direction. And yeah, there's definitely work to be done, not only in understanding which

would be the right strains say in a 3A formulation, but then also the potency testing, the immunogenicity testing, the HAIs and so forth that all have to be worked out. So, it's also not a quick step. And then we in industry would conduct the clinical trials just as we did a dozen years ago when we conducted studies of quadrivalent at the time that only trivalent was available. So, don't have an answer today, but I think as an industry, we're sincerely interested and want to work with those who are here today, as well as others in the stakeholder community around vaccines.

Dr. Chatterjee: And so, what are we looking at for a time frame to have all of that completed?

Dr. Greenberg: I'm hesitant to give a specific timeline, but you know that, and again, I'm reaching back to when industry moved from trivalent to quadrivalent, the probably phase one, two trials may or may not be needed, but if they are, they're probably going to be relatively small and quick and then phase three studies are probably going to be probably in the range of hundreds of subjects, individuals who participate. It's not to look at efficacy, which, as you know, is a much larger question, but at least confirming the safety parameters and non-inferior immunogenicity data. So, you're looking at a season or two to be able to conduct those studies. But perhaps that could be done efficiently in both the Southern Hemisphere and the Northern Hemisphere countries so that you get to the answers needed pretty rapidly.

Dr. Chatterjee: Thank you.

Dr. El Sahly: Dr. Rubin.

Dr. Rubin: Thank you. And I'm not sure who to address this to, perhaps Dr. Greenberg. But if we do move from a QIV to TIV, and with all the discussion that you were just mentioning about the possibility of introducing new antigens for a divergent A or B virus, do we lose anything in terms of the capacity to move back to QIV if we were to add another antigen? In other words,

you raised the regulatory issues. Would it be harder to make another QIV if we move to TIV, both from regulation and production?

Dr. Greenberg: Yes, thanks. Not difficult from the standpoint of manufacturing those antigens. But capacity, yes, although I. again, don't have all the answers, there could be an impact on capacity having manufacturing facilities across all the different companies running full speed for many months, working with four strains. When that reduces to three, you can see how that could, I would think, reduce capacity overall, then to ramp back up to quadrivalent is not difficult but take some planning. So, I would just remind you all that part of the rationale, justification, beyond the obvious of coverage of two B lineages at the time that the decisions were made, was that it increased capacity and that in the event of an influenza pandemic, it would generally be increased capacity to meet the challenges the demand of a pandemic. With a reduction to trivalent, you lose a little bit of that. I think we have to admit that.

Dr. Rubin: Thank you.

Dr. El Sahly: Thank you. I have a couple of questions and I'm going to try to frame them according to the points displayed on the screen for discussion. In terms of advantages of retaining the B, there is none for the public health aspect of it, the manufacturing aspect of it, and the regulatory aspect of it. Things were not nimble enough to remove. Looks like the Yamagata, at least for some manufacturers, but that is a bit concerning because this is the fourth meeting for VRBPAC where this is brought up. Although the voting directions are not sort of the only metric to follow. There was one when we were way into the pandemic. It was noted that there was little flu circulation, but of all the flus that came about, Yamagata seems to be non-present. And then it was brought up that the decline in Yamagata really began pre-pandemic. But at the time, no epidemiologic conclusion could be made because of the pandemic. Then we exited the pandemic

in a way two meetings ago, and the voting was unanimous to keep the Yamagata, but the absence of Yamagata circulation was brought up, was discussed, and pretty much everyone who voted said we will keep this vote going just in case Yamagata rears its head and to allow regulatory agencies and manufacturers time to adjust. Last meeting, the voting was 7:6, with seven keeping the Yamagata. But even the individuals who did vote to keep the Yamagata, it was precisely to allow time for manufacturers and regulatory agencies to adjust because the risk/benefit is no longer there to keep the Yamagata. But what I'm concerned about is that it seems like we are going to begin the discussion about it now with manufacturers and regulatory agencies. I wonder why this not has not taken place so far, which would have allowed that proposed timeline to either have shifted dramatically into a smaller interval or not even be there. And this question is to Dr. Greenberg and to Dr. Weir.

Dr. Greenberg:From the manufacturing standpoint, we understand and while we're aware of the discussions that took place at previous VRBPACs then I look now to Dr. Weir that well, we didn't have really substantive meetings at that time, so here we are, and we've listened and we're ready to act. But I can't reverse the past. We are where we are and we're acting. But Dr. Weir, if you have some comments as well, thank you.

Dr. Weir: Yeah, I do have a comment. I sense and feel your frustration, Dr. El Sahly, but I'd like to remind you that the VRBPAC discussions are having an effect on moving this process, whether you believe it or not. I actually think that this meeting that the WHO held this summer was a direct result of your voting in March. In fact, I'm pretty sure it had a lot to do with it. So, while I understand that you may be frustrated that it's taking a while, I do think it's having an effect, I do think it's moving the conversation forward, and I do think that you're going to see some tangible results for this at some point, and I hope the near future. So, again, I understand it.

But again, I think all of you in the VRBPAC are having an effect, and you're doing an important service by stating these concerns and stating what you think about this. I'll just leave it at that. Thanks.

Dr. El Sahly: Hey, I mean, I'm grateful you're saying that, and I think everyone on the committee is, but it looks like discussions didn't start. I mean, just judging from the presentations this morning. Okay. Dr. Janes.

Dr. Janes: Thank you. I have a question I think for Dr. Weir. I was struck by a statement that Dr. Wentworth made when he was asked about, I think the question posed to him was what could an alternative quadrivalent vaccine formulation look like and how to optimize that. What would be the framework? And I think his response was something to the effect that there's so many components to that decision. So many possible tweaks to the quadrilateral composition that it's hard to answer at this point. And he suggested that it might be easier to consider a specific proposal along those lines and that specific proposal would include both a framework for making a decision as well as a specific proposal in terms of the quadrivalent composition that's optimal under a given framework. And that really rang true to me. And so, I guess my question to Dr. Weir and others, if they wanted to weigh in on it, is who would be the party or parties responsible for proposing such a framework and such a composition? Is the onus on the manufacturers to come to the committee with a given proposed quadrivalent formulation that’s thought to provide better efficacy or is it FDA or some other entity, who is responsible for moving us forward and proposing a formulation for rethinking this?

Dr. Weir: Okay, I will give you my opinion. I think it's all of our responsibility. The flu community has a very unique track record of working together unlike almost every other vaccine. We, and I say we globally, and this includes manufacturers, includes this worldwide

network of influenza centers, collaborating centers, ERLs, and lots of academic researchers, meet periodically. We all discuss these things and including we have these discussions at our advisory committee that we're all part of. I think this is what I meant about trying to stress the need for a consensus. So, my personal opinion is that we have these scheduled meetings at least twice a year, and this is sponsored usually by the MHRA and the WHO, and we have them in July and January usually. I think that's an ideal forum to try to get some sort of consensus on how one would prioritize an alternative composition. Because I do think that you could list so many possibilities that you'll never get the data needed for everything. So, I do think that is one forum where we can do it. I think the input from the VRBPAC that we take to those meetings is important. That's what I was trying to tell Dr. El Sahly a minute ago. I think your voice does get heard. So, I think this is a combined responsibility of all of us to try to work together to see if we can make some improvement to the vaccine. I don't know if that's a great answer for you, but I really do believe it. So, I think we express those opinions here. We express them in these meetings where we all get together and we hope that we drive something toward a prioritization of what should be investigated first and start generating this data. Anyway, that's my personal view.

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

Dr. Portnoy: Thank you. I have to agree with Dr. Weir. When we voted last time to recommend that this be changed, it was really a recommendation for the process to be gone and for the discussion to occur. And it sounds to me like it exactly has. So, I think that the vote of this committee six months ago really did make a difference. I have two questions about the current influenza vaccine and one about the other about possible future vaccines. One is if the flu zones higher dose is more effective at inducing an immune response is given to older people. Why isn't

it just given to all people? Why only older people? Wouldn't younger people benefit from a better immune response also? That's my first question. My second question is, I was just wondering if there's any effort to switch the influenza over to a mRNA-based vaccine, like the Covid. I know that the legacy system is in place, and it's so much more convenient and economically feasible to continue producing influenza in chicken eggs and acellular and so on. But it seems to me that we would have a much more flexible ability to change strains if we needed to on the fly almost if we had an mRNA technology. So, I was just wondering if I could get a status update on that.

Dr. Weir: I can give you partial answers to both of those. First of all, high dose flu zone is for elderly because that's who it's indicated for. That's where the how the clinical trials were done. So, to expand that indication, there would have to be some clinical data to support it. The agency, of course, has opened anything that when someone comes in with new data. That would be up to the manufacturer to decide that that was worth exploring and then see where the data led them. I threw it out there because I thought that it was a good example of the fact that, and again, this has been brought up many times about whether one could consider increasing the amount of antigen in the vaccine. I just thought it was a good example to show that there was at least some basis to think along those lines. And while I'm at it, I'll remind you that our current vaccines for the standard doses of 15 micrograms haven't always been 15. At one point in time, before my time, they were seven and a half, and I don't remember what went into doubling it. Okay, mRNA. Yes, there's a lot of effort in this area. I'm sure that you and others have seen press releases from different companies as well as papers in the literature. Yes, there's a lot of movement toward this. Many companies are exploring mRNA platforms as a possibility for flu vaccines. When the data is there, they will come to the agency and then we evaluate them like we always do. So yes, it's very active.

Dr. Portnoy: Okay. Okay. I hadn't heard anything. So, it's nice to know that there's some movement in that direction.

Dr. El Sahly: Doctor Gans.

Dr. Gans: Thanks for giving me another opportunity. So, just along the lines of sort of how you addressed this, Hana, I think that you know, before us right now, are the advantages and disadvantages of retaining or removing the Yamagata and there really is, at least from a public health standpoint, no advantage. The only advantage we have to keeping it is to allow those individuals who would otherwise not have access to influenza vaccines, period. And so, I do think we need a better understanding is if we, as part of our Southern Hemisphere, and I think again, you were trying to get at this a little bit, Hana, what is our contribution to that access question? Because if we at this moment in time say there's really no advantage to continuing it and therefore we voted to remove it, how, I guess I'm still struggling to know the exact disruption to the market and access to other individuals since we're not as prevalent in the Southern Hemisphere production as far as I understand it and therefore that contribution is not as well understood to me, and I would really like that address better. So, I don't see an advantage except for access. So, we really need to understand what our contribution here is. We're very strongly saying, we have said for many times, we don't think there's continued advantages, and we only voted for it last time with that notion. I think there are a lot of opportunities. Dr. Wentworth goes through a very detailed evaluation of the lineages that are coming through. And clearly there's some H1N1 5A that isn't currently being as well addressed and then the 2B for the H3N2s. Those are things that I would then now like to put out to have companies and other people start looking at the advantage of having those be part of a quadrivalent. I don't know what percentage of the disease is related to these. And that would be another thing that I would love to see as we're

understanding these different, very complex array of strain types (phonetic). We would love to know what percentage so we understand, by adding that to a vaccine, what improvement we would have over what we're currently having.

And then, as been raised, not only by Dr. Weir, but just by Dr. Portnoy, I'd like to say that the other opportunities would be to look at the dosing. So, we have certain dosing that we thought was efficacious. Obviously, there are certain of these strains that actually don't do as well, and so we should be considering different dosing strategies. And then lastly, it would be really nice, I mean, as has been pointed out, if we could have other manufacturing methodology. So, if we're looking at alternative vaccines, that would be something that I would like to push forward.

And then lastly, because we've asked for this and multiple times, I mean, Dr. Wentworth clearly stated how B-cell immunity is very important for infection. We know that, and T-cell for actually clearing, but what also is immunologically important about T-cells is the breadth and depth, though it would be really nice to know if we're seeing some advantage of T-cell epitopes broadening the expansion without actually putting another strain into these. So, some of those studies that are being done as we are using that as a model for SARS-CoV-2 would be very nice to see addressed in influence on how that immunologic paradigm is being changed, not necessarily by all the different ways in which we change the vaccine, but actually by the breadth and depth of what antigenic stimulus you've seen in the past. So, those would be the directions that I would just put forth. I don't know how to be more precise without some of the data that we need.

Dr. El Sahly: Thank you, Hayley. I think you had more comments and viewpoints, but not a specific question, right?

Dr. Gans: Yeah. I mean, my real question is how specifically should we formulate our recommendations? I guess. Oh, okay, Dr. Weir, are we to give specific recommendations here or just discuss and then whenever there's a vote, we can.

Dr. Weir: Okay, so yes, obviously of these three bullets the third one is the most open-ended discussion. We're happy to hear ideas and we welcome that. I think the one that probably it would be helpful to get some specificity from the committee members is the second bullet you've heard the proposal from the manufacturers and what they think is realistic, mostly globally, but I think I would like the committee if possible, to chime in about what they think is a realistic timing for this.

Dr. Gars: And I guess, Dr. Weir, if we said now, I'm trying to understand the impact that would have on the accessibility of vaccines for the global market. That's what I'm really trying to understand.

Dr. Weir: Agree. And what I think you're sort of hearing is that the impact immediately now for the Southern Hemisphere is mostly an access availability question. The question for five months or basically Northern Hemisphere '24-'25 is more of a how much time it would take to affect these different steps, both in the US as well as the world. So, they're slightly different. Yes, if that's why I think I said at the very start of the meeting today that depending on the recommendation, we would have to go back and think through these things, too. I mean, the last thing we want to do is affect vaccine supply, even worldwide, even though our main, our main responsibility is, of course, for the U.S. So yes, it's a lot for us to weigh, but I would still like to, if possible, get specificity from the committee about what they think is realistic for the timing, if possible.

El Sahly: Well, if I may begin on that point we have already weighed in that Yamagata ought to be removed six months ago, and it would be 12 months ago, at least for the process to begin. Now, realistically, we are not in the manufacturers. We cannot expedite the manufacturing or affect it in any way. So, the question to is scientifically and from a public health standpoint when should it be removed? It should be removed a while ago, but at least now the only problem is would anyone who would have benefited from a vaccine be affected by such a decision. And that is what I don't have a grasp on. Meaning if the two manufacturers for whom we meet in the fall were to not get the opportunity to deliver their quadrivalent, would it impact any country's public health negatively, because we definitely don't want to do that. But I also wonder on the flip side of it is what would us saying now is the time to remove be what makes those wheels go in faster motion. So, for that, I would ask Dr Greenberg to weigh in, if you had time to investigate what is the contribution of these two manufacturers to the public health of the specific countries you supply. Just these two manufacturers.

Dr. Greenberg: Yes. Thank you. So, we've been able to collect some information. I don't have all the answers, but I do know that about ten countries and 10 to 20 million doses are at stake. I think it's too much to think that countries in a very short period of time, because we would be shipping vaccine as an industry to the Southern Hemisphere countries in the coming months for them to find other sources and have other contracts and have vaccine availability and the timing to help protect their populations. You know, I don't have that that visibility, but I have to think that 20 million doses lost to a handful of countries is going to have some impact to public health.

Dr. El Sahly: Yeah.

Dr. Greenberg: And although we haven't gone to PIV for the Southern Hemisphere season we're now going to move in that direction as efficiently as we can.

Dr. El Sahly: Right. I mean, the difference between 10 and 20 is significant, but okay. Dr. Cohn.

Dr. Cohn: Thanks. I just want to ask a question, I think, to either FDA or to the sub source (phonetic), but I'm wondering if there's been any research or focus groups into how the public would perceive these changes to the vaccines. I'm thinking about this from a public trust in the flu in the influenza program, especially in the U.S. given some of the challenges we've been facing with other vaccines. And I was just wondering if there's anything you guys have done in the space of how this would be interpreted publicly.

Dr. El Sahly: You mean, keeping the Yamagata or removing the Yamagata, which…?

Dr. Cohn: Removing, and how they would understand those messages around, from my perspective, this is an example of us responding to taking out things that aren't necessarily providing benefits. But if that would be sort of how it would be perceived publicly. Or if it would cause confusion and mistrust.

Dr. Greenberg: If I could just say that from our side, we're very interested in getting answers to your questions where we don't have extensive surveys that I could report to you today. We've had discussions with a lot of public health and other stakeholders, and they have really challenged us on the speed and what impact it might have in the public trust. But that's not the same as a large array of the public, of health care professionals, and others. Without question as we go through this transition, we would want to work with all of the different stakeholders to, to help with the communication to maintain the trust. So, I'm quite positive that doing nothing around communication will create some real issues for all of us to deal with. So, I would say, let's, partner together to make sure that communication is clear.

Dr. Weir: I can add in that for us, we've thought about that. And yes, I would agree with Dr Greenberg. Some sort of unified messaging approach would be best. And the issue also came up

in July at the WHO Meeting. I think everyone recognizes that it would take some effort toward messaging, but I think it can be presented as a response to public health and trying to do what's best for vaccine composition. So, I think there's way to do ways to do that messaging. But of course, the more unified the messages, the better. Over.

Dr. Sahly: I agree with Amanda, with David and with Dr. Weir as well. But if I may add also some messaging as regarding keeping the Yamagata, if that ends up being the outcome as needed Dr Pergam.

Dr. Pergam: Yeah, sorry, I need I'm still trying to clarify this in my head because there is the ability to still give the trivalent vaccine. We are approving that. So, what I'm trying to understand from industry's perspective, the southern vaccines have already been ordered, that process has begun. I'm also beginning to think ahead to our next meeting a little bit too is can the manufacturers sort of have that ability to produce significant numbers of both trivalent and quadrivalent where they would be able to give these two different places where there are different approvals in the early phases. And is that a challenge to have those two different versions like they previously did, that availability? Is that a challenge for them to be able to sort of give these two different components? So, as an example, if we decided our next round that we wanted to do, just trivalent, is that feasible within the structures that exist right now and if others decided to do the same, would that be possible to, to sort of have a slower rollout of trivalent? And then as they wait for the quadrivalent regulations and other locations to sort of be approved. I'm just trying to figure out the process of this because it feels like in some places, trivalent is already approved and that it feels like it should be an easier transition to that. I guess I'm trying to get what that looks like from a global perspective, because can we vote for two different formulations as we're talking about here, and what we already do is we vote for a trivalent

version, a quadrivalent version, is that enough to allow that process to move forward? I'm just trying to figure out how does it work from a manufacturing perspective to have those two formulations? How can you guys manage that sort of approach if that were to be something that you'd see? Like the U. S. goes in a trivalent mood, or North America is that way. What does that look like from a manufacturing perspective? I hope that makes sense. It's a complicated question, I know.

Dr. Greenberg:I was going to answer, it's a complex answer. Thanks for the question. So, a lot of that, I think is going to be better addressed by FDA. But from a manufacturing perspective, we produce the strains. The reason why I've made the point on behalf of manufacturing regarding moving to the discussion on the Northern Hemisphere for the next season is that manufacturing has already started at risk. Even now in October, we're in October. So, the process has started. There is a tremendous amount of coordination that occurs when we're speaking collectively of manufacturing of more or less around 170 million doses of vaccine and decisions are made in manufacturing facilities at an early stage, made right now as to whether the final vial filling, syringe filling is going to be a trivalent or a quadrivalent formulation. It's not something that you can decide at the last minute. So, my point on behalf of manufacturing is that for the Northern Hemisphere season through the next six months, we can move as rapidly as we can to getting the trivalent approvals, making sure all of the validation data are with the agency and they're reviewing them and approving them. We're making decisions now and in the coming weeks to months on what ends up in the filling line to then ship out starting in July. It's a process in parallel. We can work with the agency collectively as manufacturers to move towards trivalent. But at the end of the day, when it comes to filling and packaging the product to ship starting in July in the US, those decisions are made really in the next few months. So do we, as

manufacturers, can we guarantee that we're going to have all the approvals that are necessary for reactivating the, the TIV and updating the quality data and validation data. To know for sure that all we need to do is package trivalent and then ship it in July, August, September, I don't see how that's possible across the manufacturers. And so, if we were to take that risk, then I'm really worried that we would have a major shortfall in vaccine distribution next summer and fall. So, we're going to move with the agency to get the IV. I just don't see, and again, speaking for all the manufacturers, just don't see how we can guarantee that what we've packaged in vials and syringes can only be TIV and that we're absolutely guarantee that we'll be able to ship them because we haven't had the one-on-one discussions with the agency to get us to that final point. Thanks.

Dr. El Sahly: Dr. Monto.

Dr. Monto: Well, I'll start out with full disclosure. I was present at the July 13th meeting in London and actually wrote the first draft of the summary of the meeting that is circulated. And there was clearly an effect of the VRBPAC discussions and recommendations. However, at the same time, I was rather surprised that while the global influenza regulatory and recommending community had heard the concern about the continued inclusion of the B/Yamagata, the manufacturers really hadn't heard it. And there was surprised and somewhat I may say dismay at the possibility of moving very fast and that's where we first heard some of the especially regulatory concerns. I think I'd like to move to the discussion topics because they really frame what we have to do today and going over the discussion topics, the advantages of including the B/Yamagata are only, to me, being sure that we can have total synchrony in the world of switching to the trivalent formulation or whatever follows. The needs are mainly regulatory, but also logistic and I think that these need consideration but should not necessarily be the driving

force in what we do in the United States, because it looks like things may proceed at different rates in different parts of the world.

I'd also like to remember, let everybody think about the fact that we still do have trivalent vaccine being produced. And who are the countries that typically use the trivalent vaccine? It's not a clear division, but it's the more affluent countries that are currently using the quadrivalent vaccine and it's the other countries that use the trivalent vaccine. It's not a clear distinction because local manufacturer and things like that fall in. But what we're talking about here is removing a component of the vaccine, which hasn't been detected in greater than three years. Not only that, the component that we have in the vaccine is a 2013 virus and if we do have B/Yamagata reemerge from some hiding place, the likelihood of a be a 2013 virus protecting against that strain is going to be pretty low.

I'd like to move to the bullet three first before talking about the timing. At that meeting, it was clear that although we have been discussing, even in VRBPAC meetings, the alternate vaccine compositions, which might replace the current quadrivalent vaccine, there really has not been any consistent work looking at this issue. There's been work on other things, like the mRNA vaccine, but very little work on some of the simple issues about, for example, increasing the H3N2 components of the vaccine. And I had hoped that for a smooth transition, something like that would have been looked at, but very little work has been done, or at least work that we can hear about because of other considerations.

Getting to the 2nd and the key point, the timing of the possible removal. I think it's pretty clear that we can't really do that right now. The vaccine is ready to go. The manufacturing has gone on and it would be quite disruptive to move ahead. With removal right now in the Southern Hemisphere formulation. I feel uncomfortable at promising that B/Yamagata lineage would be

included in the Northern Hemisphere formulation. I think that's something we can take up at that time. I think it may be clear from our discussion and our votes that, if possible, we would like to see it removed from the Northern Hemisphere formulation, at least for the United States, because I think we're in a better position in terms of the regulatory situation to do that in the United States than many countries, which have a different system and in which the licenses for the old trivalent vaccine are not in the state that they are in the United States. And in concluding, I'd just like to circle back to the disadvantages of retaining the B/Yamagata. What I hadn't thought about before the meeting in London was the fact that B/Yamagata is in the live attenuated vaccine. We don't use a whole lot of live attenuated vaccine in the United States. But there are at least theoretical disadvantages about giving a live attenuated B/Yamagata-containing vaccine and beside that, in addition to the issue of giving something that that you don't need. Over.

Dr. El Sahly: Thank you, Dr. Monto for this summary. Dr. Wentworth.

Dr. Wentworth: Thank you. Thanks very much for your thoughtful discussion and this kind of goes back quite a little while but I just wanted to make a comment, in part from our committee's discussion at the WHO and in part because we are a collaborating center for all of PAHO (phonetic). So not just the Northern Hemisphere, but the Southern Hemisphere. There's no collaborating center from the from South America, for example yet they have many national influenza centers. They contributed very significantly to the update of the vaccine for the H1N1, for example, a lot of the viruses that I showed that were in the light blue came from South America, and I just wanted to comment that the loss of 20 million vaccine doses, so I know you feel like you kind of have an arm tied behind your back. That's a little bit the way I felt on the committee for the WHO, but it would be negatively impactful for South America, Central South America to say it had to be a trivalent. This is in part why for licensed vaccines the committee

recommended something with the components of the licensed quadrivalent vaccine B, the viruses we named which include the Phuket strain from 2013 for B/Yamagata. So I just wanted to comment there because it's very difficult to ascertain exactly how many doses when you have different companies and all of that that's going on there. But 20 million is a significant amount of vaccine used in that region. Thank you.

Dr. El Sahly: Thank you, David, for clarifying that. That is very important. Dr. Annunziato.

Dr. Annunziato: Thank you. I'm going to change my question to a comment since we're in the discussion part of the of the meeting. And I just want to reiterate what Dr. Monto said that I think what we really want to think about is the best way to get to a smooth transition from quadrivalent vaccines to trivalent vaccines and as has been pointed out in the questions and answers and in the discussion, we really want to make sure that as we are working on this that we don't have any unintended consequences that may impact, especially the most vulnerable who sometimes need a specialized vaccine or who may be in a country that has less access to a variety of vaccine manufacturers. So, thank you very much.

Dr. El Sahly: Thank you for the comment, Dr. Annunziato. I do not see any more questions or hands. We're good. Okay. Joseph, do you mind putting the voting questions on the screen? Thank you, Joseph. And I turned the meeting over now to Dr. Paydar. Dr. Paydar is going to read the voting script and conduct the voting session.

Dr. Paydar: Hi, everyone. Thank you, Dr. El Sahly, I appreciate it. Only our 13 regular members will be voting in today's meeting at this point. I do not know if Dr. Perlman is available to vote. So, we will make a note of it as we go forward. With regards to the voting process, Dr. El Sahly will read the voting questions for the record and afterwards, all voting members will cast their vote by selecting one of the voting options, which include yes, no, or abstain. You will have

one minute to cast your vote after the question is read. Please note that once you've cast your vote, you may change your vote within the one-minute timeframe. However, once the poll is closed, all votes will be considered final. Once all the votes have been placed, we'll broadcast the results and read the individual votes allowed for the public record. Does anyone have any questions related to the voting process before we begin? Joseph, could you please show the next slide?

Great. Okay Dr. El Sahly, if you could please read the voting questions. Question Number One for the record.

Question One

Dr. El. Sahly: Does the committee recommend excluding B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible? Please vote yes, no or abstain.

Dr. Paydar: Great. Thanks everyone. At this point, Joseph will move all non-voting members out of the main room for those non-voting members, please do not log out of the zoom. We'll be with you within three to five minutes. So, Joseph, please let me know when all voting members are present. Thank you.

Great. Thank you so much, Joseph. Here are the responses of the voting members for Voting Question Number One. I'll read them aloud for the public record. Dr. Perlman is not available to vote for this question. And so please note that we will have only 12 voting members for Question Number One. All 12 members have unanimously voted yes. Great, I'll read the votes allowed for the public record. Dr. Pergam? Yes. Dr. Archana Chatterjee? Yes. Dr. Arnold Monto? Yes. Dr. Andi Shane? Yes. Dr. Holly Janes? Yes. Dr. Hayley Gans? Yes. Dr. Amanda Cohn? Yes. Dr. Henry Bernstein? Yes. Dr. Eric Rubin? Yes. Dr. Paul Offit? Yes. Dr. Hannah El

Sahly? Yes. Dr. Jay Portnoy? Yes. Okay, that concludes the first question. Unanimous votes are all yes. Okay. Dr. El Sahly, if you could please read voting Question Number Two.

Question Two

Dr. El Sahly: Right. Voting Question Number Two. For the composition of egg-based trivalent 2024 Southern Hemisphere formulations of influenza vaccines. Does the committee recommend: inclusion of an A/Victoria/4897/2022 (H1N1) pandemic09-like virus; inclusion of an A/Thailand/8/2022 (H3N2)-like virus; and inclusion of a B/Austria/1359417/2021 (B/Victoria lineage)-like virus. Please vote yes, no or abstain.

Dr. Paydar: Again, for those non-voting members, please don't log out of the zoom. We'll be with you in few minutes. Joseph, please let me know when all voting members are present.

Great. Thank you so much. We have a total of 13 votes for Question Number Two. Here are the responses of each of the 13 voting members for Voting Question Number Two. Dr. Perlman has joined. I'll read them aloud for the public record. We have unanimous vote yes. 13 out of 13, a hundred percent have voted yes. There are no other votes. Thank you so much. Okay. I'll read the votes for the public record. Dr. Stanley Perlman. Yes. Dr. Steven Pergam. Yes. Dr. Archana Chatterjee. Yes. Dr. Arnold Monto. Yes. Dr. Andi Shane. Yes. Dr. Holly Janes. Yes. Dr. Hayley Gans. Yes. Dr. Amanda Cohn. Yes. Dr. Henry Bernstein. Yes. Dr. Eric Rubin. Yes. Dr. Paul Offit. Yes. Dr. Hana El Sahly. Yes. Dr. Jay Portnoy. Yes. Okay, Great. Thank you so much for your patience, everyone. Okay, Dr. El Sahly final question, if you would be so kind to read this voting Question Number Three when it comes up.

Question Three

Dr. El Sahly: Okay, and the last vote voting question for today. Voting Question Number Three for quadrivalent 2024 Southern Hemisphere formulations of influenza vaccines, does the

committee recommend: inclusion of a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus as the second influenza B strain in the vaccine. Please vote yes, no, or abstain.

Dr. Paydar: Again, for those non-voting members, please continue to be patient with us. We'll be with you in a few minutes, four to five minutes. Joseph, let me know when all voting members are present.

We have a total of 13 votes for Question Number Three. Here are the responses of each of the 13 voting members for Voting Question Number Three. I'll read them a lot for the public record. We have a unanimous vote, yes. 13 out of 13 have voted yes. For the public record, Stanley Perlman. Yes. Stephen Pergam. Yes. Archana Chatterjee. Yes. Arnold Monto. Yes. Andi Shane. Yes. Holly Janes. Yes. Hayley Gans. Yes. Amanda Cohn. Yes. Henry Bernstein. Yes. Eric Rubin. Yes. Paul Offit. Yes. Hana El Sahly. Yes. Jay Portnoy. Yes. Okay, thank you. This concludes the voting portion for today's meeting. I'll hand over the meeting back over to Dr. El Sahly for asking the committee for their voting explanation. Dr. El Sahly.

Vote Explanations

Dr. El Sahly: Yes, thank you. Thank you all for participating in today's meeting and for the votes and the lively discussion. So, I will go around the virtual table now requesting justification or commentary as to why the committee members voted the way they did, and I will go in order of appearance on the on the Zoom participants and which makes Paul Offit the first one to give his opinion.

Dr. Offit: Right. I'm not sure what more can be said. I think my vote is sort of obvious based on the data that were presented. Influenza’s a moving target. I think we're going to learn a lot moving forward in terms of how best to construct this vaccine as we have, for example, mRNA vaccines available. And as we continue to learn about this virus. I mean, I trained in a flu lab

many decades ago, and Walter Gerardo (phonetic), who was the head of that lab, said it best. He said, “If you want to research career that lasts for the rest of your life, study influenza.” I still think that's true. Thanks.

Dr. El Sahly: Very true. Thank you, Dr Cohn.

Dr. Cohn: I also think everything has been said. I really appreciate both the manufacturers and FDA's coordination and response after our last meeting around this. And I think that the way that the questions were phrased today allowed us to both push for this to happen as fast as possible, but also acknowledge and recognize that we really need to do this in a way that is beneficial and doesn't pose any unintended consequences arrests. So, thanks.

Dr. El Sahly: Thank you. Dr. Shane.

Dr. Shane: Yes, thank you very much. I agree. I think everything's been said and thank you so much for the wonderful presentations that really helped to inform my decision. I would also just echo Dr. Cohn sentiments about communication and starting to think about how we do that now in advance so that we can be best prepared. Thank you.

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

Dr. Chatterjee: Thank you, Hana. I'd like to make two points. The first one being the phrase as soon as possible. I worked with a very experienced Infection Control Practitioner, Sharon Plummer (phonetic) for many years at the Children's Hospital in Omaha, and she would often say soon is not a time. So, I would say that I would encourage all of the people that are involved to really try to identify timelines by which we should expect to see some movement on this front.

So that's the first point I'd like to make. The second I'd like to make is that sometimes, members of this committee at these meetings for the for selecting the flu strains have felt that we are nearly rubber stamping what has been put forth by the WHO, so it was very reassuring to me

to learn that our time is not wasted here that, in fact, our deliberations and discussions have meaning and importance and actually move the needle. So, I think that that is a very important function of this committee and I'm grateful for that. Thank you.

Dr. El Sahly: Dr. Monto.

Dr. Monto: Again, there's very little to add. I do like the flexibility of as soon as possible, but, there are timelines that have been discussed, and I think we need to try to see whether it's possible to do it in the United States, at least by the time we meet next March, because it's going to it's very clear that the whole world may not be moving in synchrony to the trivalent vaccine. I also am delighted that we are not voting on each antigen separately as we have in the past. Thank you.

Dr. El Sahly: Dr. Gans.

Dr. Gans: Thank you. Of course, the conversation has been robust, but I guess what I'm reminded is that despite conversations, there does seem to be quite reactive and not proactive stance from many of the authorities that are dealing with this. It's very complex, we understand that, but I would say and just echo that we're going to be back here in March to make another vote. I would just really urge people to start looking at other options by that period of time so that we're not in the situation where we would deny access to any individual. That's really where the votes I think are coming from today is to really ensure that globally, people have the resources they need to have health as we would all hope. I do think it's very important for the public to realize that the safety of all of the options that are before them is very strong and that there's really no issues with that, and that wasn't a consideration today, of course. I would urge the people who can look at this to look at the different strains. We've already highlighted two with 5A in the H1 and the 2B in the H3 that seemed to be having decreased antibody responses

as well, there's reduction to those particular strains, and there does seem to be some signal around the country as was well outlined, and I would also urge, because it seems that we need to do that looking at other formulations that have already been described messenger RNA, so that we're not really stuck with these kinds of timelines and I think I'll stop there. Thank you.

Dr. El Sahly: Thanks. Dr. Bernstein.

Dr. Bernstein: Sure. I don't really have a whole lot more to say other than flu is a global disease and I do think that flu is a global disease and I think it's important that we emphasize communication, which will be incredibly important. I think messaging must be very clear. I think regulatory issues need to be addressed in a timely way. And I think manufacturing issues also, will need to be managed. I do think it's a positive thing for the public to appreciate that ongoing continuous evaluation of vaccine-preventable diseases happens and this is a perfect example of that. Otherwise, I really don't have much else to add.

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

Dr. Janes: Thank you. I guess my focus has been on, I think I'm in agreement of all the comments that have been said about how obvious it was around the decision to recommend for this particular question, removing B/Yamagata as soon as possible, but that's really a sort of special case of the larger decision around how should the strain composition be decided on an annual basis. And the issues that have been raised today around the complexity of that decision, the complexity of regulatory and manufacturing issues and the need to prepare well in advance around any compositional changes really raises to me the importance of advancing and advocating for urgent discussions around what is the framework for deciding on that strain composition for future vaccines? So, it was gratifying to hear the outcomes or the implications of the VRBPAC discussions on WHO consultations and other consultations that have been

happening over the preceding year, and I guess I would just suggest that this committee again can perhaps have an impact in terms of advocating for using the future biannual flu meetings that Dr Wentworth mentioned to really begin to align stakeholders around frameworks for deciding compositions of future vaccines, because in parallel, these manufacturers will need to be communicating with regulatory authorities around the clinical packages that will need to be provided to support annual regulatory decision making. So it appears that there is quite a bit of work in the academic sphere along these lines, but a lot to be done again to bring the multiple stakeholders on board and gain consensus so that our committee and other committees considering strain recommendations on an annual basis can have specific proposals put in place for us for future years. So, thanks. Thanks. Dr. El Sahly, that's all for me.

Dr. El Sahly: Thank you. And Dr. Portnoy.

Dr. Portnoy: Great. Thank you. I agree with Dr. Chatterjee that it's reassuring to think that the decisions that this group made actually had a difference in the discussions about viral composition. So, that that is reassuring. These viruses move fast. They move very quickly. They mutate and so on. And we have to learn to change just as fast as they do if we're going to use vaccines as a way of controlling and keeping these viruses under control. I think it's really important that we change the way we consider developing vaccines, approving vaccines, and studying vaccines. I think this whole process needs to be sped up because the viruses are not going to wait for us. And if we want to use vaccines to treat them, we have to change the way we do things too. But it's great to be part of a group that's involved in making those decisions. Thank you very much.

Dr. El Sahly: Thank you, Jay. I think I'm the last voting member. The justification for the first two questions. The way the vote, at least my vote went was obvious and deliberated the between

this and previous meetings. The voting on the third question was the one with a bit of trepidation and back and forth. However, with the uncertainty regarding what those 10 to 20 million doses are going to do and in order to avoid harming anyone by such a decision, I voted to keep the quadrivalent. However, we will be reconvening in six months, and it wouldn't be the first time an influenza strain disappeared. H2N2 did the same and looks like Yamagata is also heading out and that began pre-pandemic and the process between regulatory and manufacturing should take that into account which would be really what makes the confidence in vaccine and vaccine uptake be stronger. And with that I think, oh, I think I forgot Steve Pergam. So, I'm not the last. So, the last word goes to Steve Pergam. And I really didn't, I really didn't.

Dr. Pergam: That's okay. That's okay. You have a lot of plates. Don't worry. I'm not offended. I think I didn't really want the last word because there's so much that's been said and I think this is a great discussion today, I think it was really valuable. I think the one thing and that I would really encourage FDA and industry is to begin to start planning some studies on how are they going to look at new formulations of quadrivalent vaccines start that discussion now because this is already you know the I think the second year we've had this discussion and I think there's a definitely some interest in pursuing new directions. So, I think you've heard from all of us that we'd like to see the changes coming in the future. So, I think beginning to plan those studies and about being able to bring some data back to us about what other opportunities might exist will be really important. And I think as one of my colleagues said, developing the framework for what that's going to look like is going to be really important. So, I think we all are excited about the directions this is going, and I think this just shows how important the global work that goes into this, into vaccine development, and I think it's a great model for future vaccines in the future too.

Dr. El Sahly: All right. Thank you, Steve. So, and hopefully when we reconvene in six months, the issue of the B/Yamagata would be behind us. That's hopefully enough time to move on. With that, I turn the meeting over to final comments from the FDA.

Closing Comments

Dr. Weir: I have a couple of comments. One is just a big thank you to all of you. It has been a good discussion and I really think we all value your input. My take from the discussion was that there was, while everyone agreed with the ASAP, as soon as possible phrase I think everyone also realized that that was not practical for right now, the Southern Hemisphere. But I did get the impression from several comments that the committee wasn't quite ready to give up on ’24, ‘25 Northern Hemisphere yet, and that we have a few months to keep working on this. And I was pleased to hear the manufacturers say that they wanted to work with us all to see what they could do even without any guarantees. So, I think the burden is on us to do that work to see what we can do. I also heard that everyone was enthusiastic about trying to come up with ways to improve the vaccine with other formulations. And again, though, I got the message that what the committee would like to see is some results from the next time to try to hear something that's being done to actually try to make this happen. So, I think that's another take home message that all of us heard. And once again, I would like to thank David Wentworth for all he's done for the last four or five years, and welcome Rebecca Condor (phonetic) for future meetings like this. Once again. Thank you Dr. El Sahly and all of the rest of the committee. I think you did a great job. Thank you very much.

Dr. El Sahly: Thank you, Dr. Weir. Dr. Paydar, would you be the one adjourning the meeting?

Adjournment

Dr. Paydar: Yes, for closing comments, I just wanted to thank the committee and CBER staff for working so hard to make the meeting a successful, productive meeting. I now call the meeting officially adjourned at 1:20 p. m. Eastern time. Have a wonderful rest of your day. Thank you.

Bye.