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Center for Biologics Evaluation and Research (CBER)

187th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Open Session

Zoom Video Conference

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Call to Order and Welcome

Dr. El Sahly: Good morning, everyone. I would like to welcome you to the 187th meeting of the Vaccines and Related Biological Products Advisory Committee. During the meeting today, we will be discussing three topics. The first topic on the discussion is the strain selection for the influenza virus vaccines for the 2025 Southern Hemisphere influenza season. I would like now to welcome Kathleen Hayes, who is the designated federal officer for the meeting today. Kathleen.

Administrative Announcements

Ms. Hayes: Hi, good morning. Good morning, everybody. My name is Kathleen Hayes and I will be serving as the designated federal officer for today's 187th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA Center for Biologics Evaluation and Research, and the committee, I'm happy to welcome everyone to today's virtual meeting. Under topic one, the committee will discuss and make recommendations on the strain selection for the influenza virus vaccines for the 2025 Southern Hemisphere influenza season. Under topic two, the committee will discuss pandemic preparedness for a highly pathogenic avian influenza virus, including considerations for vaccine composition for H5 vaccine. Under topic three, under open session, the committee will hear an overview of the research program in the Laboratory of Pediatric and Respiratory Viral Diseases, and the Laboratory of DNA Viruses, and the Division of Viral Products within the Office of Vaccines Research and Review in CBER.

Today's meetings and topics were announced in the Federal Register Notice that was published on Thursday, September 19th, 2024. At this time, I would like to acknowledge our leadership, if we could go to the next slide. Dr. Peter Marks, Director of CBER, along with doctors David Kaslow, Jerry Weir, and Sudhakar Agnihothram, with the Office of Vaccines. And on the next slide, I would like to introduce and acknowledge my Division Director, Dr. Atreya,

along with the VRBPAC team whose contributions have been critical for preparing for today's meeting. And this includes Dr. Sussane Paydar, Ms. Joanne Lipkind, and Ms. Lisa Johnson.

On the next slide, I would like to express our sincere appreciation to the AV team, Gideon McMullin, and Dion Wren in facilitating the meeting today. And the transcriptionist for today's meeting is Catherine Diaz from Translation Excellence. For questions, please feel free to contact FDA's Office of Media Affairs at fdaoma.fda.hhs.gov.

Roll Call & Introduction of Committee Members

We'll begin today's meeting by taking a formal roll call, with the next slide, for the committee members and the temporary voting member. When it's your turn, if you could please turn your video on, unmute your phone, and then state your first and last name, organization, and area of expertise. Then when finished, you can turn your camera off and we'll proceed with the next person. We will start with our chair, Dr. El Sahly.

Dr. El Sahly: Good morning, everyone. My name is Hana Sahly. I am an adult infectious diseases physician at Baylor College of Medicine. My research focuses on clinical vaccine development.

Ms. Hayes: Thank you. Next slide. We will go to Dr. Berger.

Dr. Berger: Hi, my name is Adam Berger. I'm the Director of Clinical Healthcare Research Policy at the National Institutes of Health. I'm a geneticist with additional training in immunology. Thanks.

Ms. Hayes: Thank you. Dr. Bernstein.

Dr. Bernstein: Good morning, everyone. My name is Hank Bernstein. I'm a pediatrician at the Zucker School of Medicine at Hofstra Northwell, a professor of pediatrics there. And my expertise is in vaccinology and infectious diseases. Thank you.

Ms. Hayes: Thank you. Dr. Chatterjee.

Dr. Chatterjee: Good morning, everyone. I'm unable to start my video because it says the host has stopped it, but it is my honor and privilege to serve as the dean of Chicago Medical School. I am a pediatric infectious diseases specialist by background and training, and I specialize in the area of vaccines.

Ms. Hayes: Thank you, Dr. Chatterjee. Next slide. Dr. Gans, please.

Dr. Gans: Good morning. I'm Hayley Gans, Professor of Pediatrics and Pediatric Infectious Disease at Stanford University, and I am the Director of Pediatric Infectious Disease Program for Immunocompromises. And my research is in the immune response to that.

Ms. Hayes: Thank you. Dr. Jódar, the industry representative. I believe he just joined, so let's come back to him in just a moment. Dr. Monto.

Dr. Monto: I'm Arnold Monto. I'm at the University of Michigan School of Public Health, where I work on epidemiology of infectious diseases, with a particular emphasis on prevention through vaccines and their use.

Ms. Hayes: Thank you. Dr. Jódar, if you have your audio connected, can you introduce yourself?

Dr. Jódar: Yes, I'm Luis Jódar. I'm the Chief Medical Officer for vaccines and the infectives at Pfizer, and I represent industry in this third-party meeting. Thank you.

Ms. Hayes: Thank you. Next slide. We will have Dr. Offit.

Dr. Offit: Good morning. I'm Paul Offit. I'm a professor of pediatrics in the Division of Infectious Diseases at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. My areas of interest are mucosal vaccines and vaccine safety. Thank you.

Ms. Hayes: Thank you. Dr. Perlman.

Dr. Perlman: Yeah, I am Stanley Perlman, at the University of Iowa. I'm a pediatric infectious disease expert and a microbiologist studying coronaviruses.

Ms. Hayes: Thank you. Dr. Portnoy, the 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 attending physician in allergy immunology at Children's Mercy Hospital here in Kansas City, Missouri.

Ms. Hayes: Thank you. And Dr. Rubin.

Dr. Rubin: Hi, I'm Eric Rubin. I'm at Harvard, the Brigham and Women's Hospital and New England Journal of Medicine, and I study tuberculosis.

Ms. Hayes: Thank you. And on the next slide, we have our temporary voting member, Dr. Wharton.

Dr. Wharton: Good morning. I'm Melinda Wharton. I'm Associate Director for Vaccine Policy at the Centers for Disease Control and Prevention. I trained as an adult infectious disease physician and have worked in vaccine programs at CDC for many years. Thank you.

Conflict of Interest Statement

Ms. Hayes: Thank you. Thank you, everyone, for the introductions. Next slide. For today's meeting for topic one, we will have a total of 12 participants, which includes 11 voting and one non-voting member. And I will now proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record. The Food and Drug Administration is convening virtually today, October 10th, 2024, for the 187th meeting of the Vaccines and Related Biological Products Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as the chair for today's meeting.

The VRBPAC committee will meet in open session today under topic one to discuss the strain selection for the influenza virus vaccines for the 2025 Southern Hemisphere influenza season. This topic is determined to be a particular matter involving specific parties. Under topic two, the committee will meet to discuss pandemic preparedness for highly pathogenic avian influenza vaccines, including considerations for vaccine composition for H5 vaccine. This topic is determined to be a particular matter involving specific parties. Under topic three, the committee will hear an overview of the research programs in the Laboratory of Pediatric and Respiratory Viral Diseases, and the Laboratory of DNA Viruses and the Division of Viral Products within the Office of Vaccines Research and Review in CBER. Per agency guidance, this session is determined to be a non-particular matter which would have no impact on outside financial interests. And for topic three, no external affected firms or entities were identified, and members were not screened for this topic. After the open session is completed, the meeting will be closed to the public to permit discussions where disclosure would constitute an unwarranted invasion of personal privacy. With the exception of the industry representative, all standing and temporary voting members of VRBPAC or appointed as special government employees or

regular government employees, brought in 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 limited to 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGE and SGE consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and loyalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflict of interest when it's determined that the agency's need for a special government employee’s services outweighs the potential for a conflict of interest created by the financial interests 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 service which the government may expect from the employee. Based on today's agenda, and all financial interests reported by the committee members and consultants, there have been no conflict-of-interest waivers issued under 18 U.S.C. Section 208 in connection with this meeting.

We have Dr. Melinda Wharton from CDC serving as a temporary voting member. Dr. Luis Jódar from Pfizer will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees, and serve as non-voting members of the committee. They do not participate in any closed session of the meeting. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee. Dr. Jay Portnoy is serving as a consumer representative for this committee meeting. 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 and can attend the closed session. Disclosure of conflict of interest for speakers and guest speakers follows applicable federal laws, regulation, and FDA guidance. The guest speakers for this meeting include Dr. Todd Davis, acting chief in the virology, surveillance and diagnosis branch within the influenza division in the National Center for Immunization and Respiratory Diseases at the Center for Disease Control and Prevention. Dr. Rebecca Kondor, interim director, WHO Collaborating Center for Surveillance and the National Center for Immunization and Respiratory Diseases at the Center for Disease Control and Prevention. And Dr. Christine Oshansky, director of Pandemic Vaccines and Adjuvants Program and the Influenza and Emerging Infectious Diseases Division at the Biomedical Advanced Research and Development Authority.

FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial relationship that they may have with any affected firm, its products, and if known, its direct competitors. We would like to remind standing and temporary members that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to

inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the conflict-of-interest statement for the public record. And I would like to hand the meeting back over to Dr. El Sahly. Thank you.

Introduction to VRBPAC Meeting Topics – Dr. David Kaslow

Dr. El Sahly: Thank you, Kathleen. Now I would like to invite Dr. David Kaslow. Dr. David Kaslow is the director, Office of Vaccine Research and Overview at CBER FDA. Dr. Kaslow will do the introduction of VRBPAC meeting topics today.

Dr. Kaslow: Thank you, Dr. El Sahly. And on behalf of the Office of Vaccines Research and Review, let me also welcome all to this 187th VRBPAC convening, where three topics will be covered. Next slide, please. So today we're going to ask VRBPAC to consider the following topics. The first one I think is well known to VRBPAC this time of year, and that is the discussion, recommendation, and vote on the seasonal influenza vaccine, Southern Hemisphere strain selection for the two egg-based vaccines licensed in the U.S. We will then ask the committee to turn its attention to non-seasonal influenza vaccine, specifically the highly pathogenic avian influenza, and considerations for pandemic preparedness in this inter-pandemic period. And then the final topic for today is associated with recent site visits of the Laboratory of Pediatric and Respiratory Viral Diseases, and the Laboratory of DNA Viruses in OBRR's Division of Viral Products. Next slide, please. So, for the first topic, we will start with a brief introduction to the coming year Southern Hemisphere strain selection by Dr. Weir from FDA, and that will be followed by a presentation and a Q&A with Dr. Kondor, from CDC, on global seasonal influenza virus surveillance and characterization. And as there were no submissions for open public hearing, we will ask VRBPAC to then discuss, recommend and vote on two questions. Next slide, please.

The first is a question on a composition of egg-based trivalent Southern Hemisphere 2025 formulations, in which a new strain for H3N1 is under consideration. And the second question considers the inclusion of B. Yamagata lineage, and the quadrivalent Southern Hemisphere 2025 formulation, for those jurisdictions outside the U.S. where a quadrivalent seasonal influenza vaccine supplied by two U.S. manufacturers are in use. Next slide, please. We will then turn to topic two, pandemic preparedness for highly pathogenic avian influenza, and in particular, H5 influenza vaccines. Next slide, please.

Shown on this slide is the strain change process described by Weir and Gruber in 2016. The concept was that, building off of a U.S. licensed seasonal influenza vaccine for which there was demonstrated clinical efficacy, a manufacturer of a U.S. licensed seasonal influenza vaccine could license a subtype-specific prototype pandemic influenza vaccine, such as H5N1, based on clinical safety and immunogenicity, with effectiveness inferred from the efficacy of the seasonal vaccine. Implicit in this model was that, as the prototype pandemic vaccines were updated, and additional safety and immunogenicity accrued with those updated prototype vaccines, a manufacturing strain change supplement would suffice, if and when a pandemic occurred. Next slide, please.

To take advantage of the inter-pandemic period to accrue additional safety and immunogenicity evidence with the updated prototype vaccines, we are now asking VRBPAC to consider a model where accrual of that additional evidence with the updated prototype vaccine is made explicit. The proposed process has at least two advantages. First, it provides a larger evidence base for relying on manufacturing strain change supplement, during the urgent response to a pandemic. And second, with ongoing inter-pandemic updates to the prototype vaccine, coupled with better and better tools to forecast effective pandemic vaccine composition, we may

save critical pandemic response time by having the updated vaccines when we need them, without waiting for a strain change. Next slide, please.

So, with that proposed model in mind, we will ask our chair, Dr. El Sahly, to call the meeting to order and call upon Dr. Weir again to formally introduce topic two. After that introduction, we will again go to a CDC colleague, Dr. Davis, to review H5 virus surveillance and characterization in the U.S. and globally, as well as review recommendations for candidate vaccine virus development. After which Dr. Oshansky will provide an overview of BARDA's Pandemic Influenza Preparedness and Response Program. And again, as there were no submissions for the open public hearing, we will then ask the committee to discuss two topics. Next slide, please.

First, to discuss the proposed strain change process during the intra-pandemic period. And second, apply that discussion to the current inter-pandemic period, specifically whether an update to the current licensed H5N1 prototype vaccines is needed, and whether the candidate vaccine viruses are available to appropriately update licensed prototype H5 vaccines. Next slide, please. And then turning to our third topic on our intramural research programs. Next slide, please.

The agenda for topic three, we'll start with the roll call and statements of conflict by our designated federal officer, Ms. Hayes. Dr. Elkins will then provide an overview of CBER research programs, followed by Dr. Merkel, who will provide an overview of research in the Office of Vaccines Research and Review and the Division of Viral Products. Dr. Ye, the lab chief of LPRVD, will then provide an overview of research in his lab, followed by Dr. Peden, the lab chief of the Laboratory of DNA Viruses, who will provide an overview of the research in his

laboratory, after which VRBPAC will meet in closed session for discussion, recommendations, and voting. Next slide, please.

As I noted at our last VRBPAC meeting, I again want to emphasize the vital role and contribution that our intramural research regulators contribute to OBRR. These are active bench research scientists who do regulatory use-inspired research, and have additional training needed for product review. This is a role unique to the agency, as these scientists contribute both to regulatory use-inspired research as well as product review. You will hear today from two of the 11 laboratories in our product and research divisions. Next slide, please.

So let me conclude by again welcoming all, and by thanking the committee members, including our temporary voting member, for your time preparing for and participating in today's meeting. By thanking today's FDA, CDC, and BARDA presenters. By thanking those from FDA who helped prepare for and organize this meeting. And by thanking those of you who have joined this open public meeting virtually. We look forward to a productive triple topic meeting today. And with that, back to you, Dr. El Sahly.

Introduction to Seasonal Influenza Vaccine Strain Selection Southern Hemisphere 2025 – Dr. Jerry Weir

Dr. El Sahly: Thank you, Dr. Kaslow. To introduce the seasonal vaccine strain selection, Southern Hemisphere 2025, I'd like to introduce Dr. Jerry Weir. Dr. Jerry Weir is the director of the Division of Viral Products at the OBRR CBER FDA. Dr. Weir.

Dr. Weir: Thank you and good morning. Welcome everyone to our annual strain selection for the Southern Hemisphere. Can we have the next slide? Okay, so as you've already heard, the purpose of this first session of the VRBPAC is to make recommendations for the strains of influenza A, H1N1, and H3N2 and B viruses to be included in the 2025 Southern Hemisphere

formulation of influenza vaccines licensed in the United States. The reason for this is that since 2016, we now have two U.S. vaccine manufacturers who have been approved to produce Southern Hemisphere formulations of their influenza vaccine. These are Sanofi's Fluzone and Securus Azalea. Both of these vaccines are quadrivalent and produced in eggs. And as you know, from me doing this many times, our strain recommendations and supplement approval for the Southern Hemisphere formulations follows the Northern Hemisphere process, using the most recent WHO recommendations as a guide. So I'll briefly remind you where we are today from the last couple of meetings. Next slide.

We most recently met in March of this year, to make recommendations for the Northern Hemisphere vaccines for 2024-25, the season we're just now entering. At that March 5th meeting, the VRBPAC recommended only trivalent formulations for 2024-25 influenza vaccines in the U.S. for the following strain compositions. I'm not going to read them all now, but at that meeting, we made, again, egg recommendations for egg-produced viruses and cell and recombinant viruses. And again, the committee recommended only trivalents for use in the United States. And indeed, that is all that is available in the United States this year, based on the VRBPAC and FDA recommendations. But because quadrivalent influenza vaccines were and are still distributed in other parts of the world, at that March meeting, the VRBPAC recommended inclusion of a B/Phuket/3073/2013 Yamagata lineage-like virus as the second influenza B strain in the vaccine for U.S. licensed quadrivalent influenza vaccines intended for ex-U.S. distribution. So, that's where we were in March.

If we go to the next slide, you will see the most recent WHO recommendation, which was made a little more than a week ago, for the Southern Hemisphere influenza vaccines for 2015. In this recommendation, the WHO recommended the trivalent egg-based vaccines for use in the

Southern Hemisphere influenza season containing an A/Victoria/4897/2022 H1N1 pmd09-like virus, an A/Croatia/10136RV/2023 H3N2-like virus, and a B/Austria/1359417/2021 B/Victoria lineage virus. The A/Croatia/H3 recommendation was new compared to the most recent Northern Hemisphere recommendation that I just showed you. Again, the WHO recommended for the B/Yamagata lineage component of quadrivalent influenza vaccines remains unchanged from previous recommendation, and this includes a B/Phuket/3073/2013 B/Yamagata lineage-like virus. And so, that is the most recent WHO recommendation, and that's where we will start our discussion and recommendations today, and that's shown on the final slide. Next slide.

These will be the voting questions for the committee, and again, we always break this down into two components. One, we just do a single question for the committee for egg-based trivalent vaccines, because again, the manufacturers in question, in this case, are all egg-based vaccines. And we'll ask for the same WHO recommendation of the A/Victoria pdm09, the A/Croatia H3N2, and the B/Austria. And then again, because these manufacturers are producing for the Southern Hemisphere, and these regions of the world are still using quadrivalents, we'll ask the committee to recommend whether they recommend an inclusion of a B/Phuket/3073/2013 B/Yamagata lineage-like virus, as the second influenza vaccine strain in these vaccines. And that's it for the introduction. If anyone has any questions, I'm happy to try to clarify. Over.

Introduction to Seasonal Influenza Vaccine Strain Selection Southern Hemisphere 2025 – Dr. Jerry Weir – Q & A

Dr. El Sahly: Thank you, Dr. Weir. Yes, I have a brief question, and I'd like to invite my colleagues to use the raise hand function should they have a question. So, since for regulatory reasons, the ex-U.S. program couldn't get rid of the fourth strain yet, why not then have it as one

voting question? I mean, is it consequential that we vote on the second question? I mean, they need the vaccine, they're not there yet. Let's just put the four of them together.

Dr. Weir: You're probably right, Dr. El Sahly. We could have changed it. I am somewhat guided by convention. We've kind of always done it this way.

Dr. El Sahly: It's okay.

Dr. Weir: So I left it like this.

Dr. El Sahly: Okay.

Dr. Weir: But it does also give the option, if manufacturers over the coming year, before next summer, actually do have markets where they produce both, I will have a separate recommendation specifically for the trivalent. In other words, they couldn't put the B/Phuket into the trivalent. So, in some ways it makes it a little cleaner. Over.

Dr. El Sahly: Alright. Fair enough. Any other questions to Dr. Weir? And there are no raised hands. Thank you, Dr. Weir. I'd like to introduce our colleague from the CDC, Dr. Rebecca Kondor, Interim Director, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, the lead of the Genomic Analysis Team, Virology, Surveillance and Diagnosis Branch, Influenza Division, National Center for Immunization and Respiratory Diseases. Dr. Kondor will go over the information for the Global Seasonal Influenza Virus Surveillance and Characterization. Dr. Kondor.

CDC: Global Seasonal Influenza Virus Surveillance and Characterization

Dr. Kondor: Thank you. Good morning. I'll just get a second for my video to update. Thank you. Okay, great. Well, it's my pleasure to be able to give the comprehensive update for the virus

surveillance and characterization. Next slide, please. So this data represents the WHO Vaccine Consultation Meeting that was held for the Southern Hemisphere 2025 influenza vaccine. The consultation includes data from the continuous surveillance conducted by the Global Influenza Surveillance and Response System, and includes several partners through WHO, the WHO Collaborating Centers, the National Influenza Centers, the WHO Essential Regulatory Labs and also our WHO H5 Reference Laboratories. The meeting occurred the 23rd to the 26th of September in Melbourne, Australia, and was chaired by Ian Barr, the Deputy Director of the WHO Collaborating Center in Melbourne. There were 10 advisors, which are the directors of the Collaborating Centers in Essential Regulatory Labs, as well as 45 observers from the listed institutions. Next slide, please.

So, here's a link to the WHO vaccine recommendations, that Dr. Weir has already presented, that, compared to the Northern Hemisphere 2024-25 and the previous 2024 Southern Hemisphere, there was only one antigen recommended to change, and that was the H3N2 virus antigen. And then we'll go to the next slide. These are links for all of the documents coming out of the vaccine consultation meeting, where you can find additional information. Next slide, please. So, another overview of what type of information goes into the vaccine selection process, and really, we're trying to identify an influenza virus antigen that will confer a breadth of immunity across the multiple subclades and genetic variants that we're detecting in our surveillance, to really reduce the risk. So, not just trying to be perfect in identifying what virus could be circulating six months to a year later. So, the data that I'll present will address whether there were significant epidemics and where and when were they. Also to understand the genetic diversity of the viruses from both influenza A and B, which circulated. Also looking within those genetic clades for specific amino acid changes on the surface proteins, understanding whether or

not there's been antigenic drift, through a couple of different assays. And this is looking at that antigenic drift through both their anti-serum and also post-vaccination human serum. And then looking at the proportions of the genetic variants and whether we can observe trends in which clades are increasing or decreasing in their global circulation, and understand which may be likely to predominate.

And lastly, do we have available vaccine candidates that will actually confer protection, a breadth of protection, across the genetic diversity that we're seeing? Okay, next slide, please. So this is a long list of different data that's used, and I'll let you go back and read this separately. But just wanting to say that it's very comprehensive in terms of the data that's presented during these meetings. And I won't do it justice in terms of how quickly we'll go through that. But for each subtype, I'll describe at least the main highlights that led to the decision. Next slide, please.

This map addresses where we were able to have specimens and genetic data, and antigenic characterization data, from the Global Influenza Surveillance and Response System, showing very large amounts of geographic representation in the data used in this analysis. And this analysis really focuses in on viruses collected February first through the end of August, 2024. And next slide.

This summary from the WHO FluNet reported data shows the type and subtype of influenza viruses reported by the GISHRS National Influenza Centers. And we can look at the very end of the graph, into 2024, to see where we've been since I last updated this committee in March. We've seen a shift in the type, from predominantly type A, before March of 2024, to more influenza B detections, all B/Victoria, since 2024. And as we go into the summer months of the Northern Hemisphere, so the 2024 Southern Hemisphere season, we see a co-circulation of

influenza H1N1 and H3N2, predominating, and detections of influenza B, but quite smaller amounts. Next slide, please.

This graph shows the genetic characterized viruses by the collaborating centers, comparing the past four Southern Hemisphere seasons. And we can see a large amount of genetic sequence data for both the H1N1s, H3N2s, and B/Victoria viruses. And again, because no B/Yamagata viruses were detected, there were no genetic data available for that. Next slide, please. The main responsibility of the WHO collaborating centers are to perform antigenic characterization. And this shows the amount of viruses that had antigenic characterization performed by the collaborating centers. Again, seeing a large amount of data across all three viruses presented here. Okay, next slide. Now we'll get into the H1N1 PM09 virus characterization data. Next slide, please.

This map shows the viruses detected in the global influenza surveillance and response sentinel surveillance, as a proportion of the total positives. And so, where we're seeing the darker yellow, orange, and red, are higher proportions due to H1N1. And since this includes February to August, we're seeing the tail end of the Northern Hemisphere and the full Southern Hemisphere season. And if we want to focus in on the Southern Hemisphere season, we see influenza H1N1 pmd09 detected in all regions of the Southern Hemisphere, and particularly in South America, parts of Central and South Africa, Southeast Asia, and parts of Oceania. Next slide, please.

This is a large phylogenetic tree, going a temporal route, with data collected back to 2022. And we're using this information to see how the genetic clades are evolving and spreading. So, we're using temporal data by a color of the marks next to the tree, to look at what region of the world virus was collected by. And we're using time axes to show which clades are increasing in proportion over time. And what we're seeing is a continued co-circulation of the 5A2A

subclades. So 5A2A and 5A2A1 are our major clades. And we've split these further into subclades. So 5A2A will have C subclades, C.1 through C.9, and 5A2A1 will have D subclades, D.1 through D.4. We're splitting this up into smaller subclades in order to look for a more granular level of clade diversity and proportion changes over time.

And what we'll be able to see on the next map, next slide, please, is a change in the proportion of these new subclades that we are showing here. On the left, you see viruses collected in September through January. So primarily the Northern Hemisphere season. And in that, we're starting to see a little bit of regionality differences, in that the 5A2As are seen primarily in Europe, North Africa, and Asia, and Southeast Asia, where 5A1s were primarily in North America. If we switch to the right, looking at collection dates of February first through August 31st of 2024, we're again seeing this regional difference. More viruses from the 5A2 were detected in North America, Central and South America, compared to the rest of the regions. And the majority of the viruses that circulated outside of the Americas were from the 5A2C subclades, specifically the C.1.8 and the C.1.9. And now we'll look into the genetic and antigenic properties of these viruses. Next slide, please.

So this is a bar graph showing the total viruses that had antigenic characterization, by the different collaborating centers, over the Southern Hemisphere periods. And we can see that all collaborating centers received H1N1 viruses and presented data used in this analysis. Next slide, please. This table summarizes the antigenic analysis for H1N1s using HI assays and post-infection ferret antiserum. So we've raised ferret antiserum to our two vaccine virus antigens. For the cell, we have A/Wisconsin/67/2022. And for the egg-based, an A/Victoria/4897/2022. This shows the categorization of the antigenic results, as either like, meaning the full reduction against the homologous antigen, was less than eightfold. Or low, showing an antigenic drift with a result

of an HI greater than eightfold reduction in HI titers. If you look at between collaborating centers, and in the total, overall we're seeing very few viruses characterized with a low greater than eightfold reduction in HI titers. So, throughout the genetic diversity that each of these collaborating centers received and tested, we're not seeing an increase in antigenic drift through ferret antisera raised to either the cell or the egg. Next slide, please.

So here's an example of the CDC's integrated genetic and antigenic data, where we're now asking the question, when we look at the phylogenetic tree shown on the left, and we're looking here about what are the molecular determinants of any antigenic change that we may be seeing in our antigenic characterization assays. So, we have the phylogenetic framework, which helps show specific mutations that a particular subclade may have, in the hemagglutinin protein. And then we confer the results of the antigenic information on the right with a heat bar, showing the full reduction in the HI assay. And what we've done is split it out into the categories I mentioned, as like being less than eightfold, and low being greater than or equal to eightfold. And this is where we can look to see whether a specific subclade with changes in the hemagglutinin shows a different pattern of recognition by our ferret antisera in HI. And, as I mentioned, there's two majors circulating clades, the 5A2A and the 5A2A1, each with their own specific additional subclades. However, we're not seeing any antigenic drift to any of the particular genetic subclades that I've mentioned before. And this is represented by a large amount of yellow on the tree, heat map, next to the tree, and very few viruses with reductions. So we're seeing good coverage of the ferret antisera raised against the Wisconsin/67/2022 vaccine reference viruses. Next slide, please.

And we also want to show how this looks over time, with our antigenic cartography. So the data shown, created from the HI assays, is then put in a map where each of the squares

This shows results from virus neutralization assays. We're seeing a lower proportion of viruses that had greater than 8-fold reductions in virus neutralization titers, but, again, still detecting viruses with reduced neutralization titers, so antigenic changes are still being seen by our virus neutralization assay. And we'll go through a little bit of where we're seeing these particular changes in the next slide, when we look at our integrated phylogenetic and genetic and antigenic data.

Okay, so this is, again, where we're trying to understand the genetic diversity, and in which particular subclade and amino acid changes in the surface protein could be showing us the antigenic drift. I'm showing the results of the HI assays from the WHO Claverin Center at CDC. And what we can see across the J.1 and the J.2 viruses, that make up the bulk of the virus antigens tested in our assays, is J.1s were fairly well recognized by the ferret antisera, to Massachusetts/18/2022. However, in J.2, we're starting to see an increase in viruses with reduction, or in poor reactivity, with the ferret antisera. And if we looked at the molecular changes that are occurring in the hemagglutinin, we're seeing patterns of changes at positions 145, 158, or 189, or combinations of these changes, being more responsible for the antigenic drift detected by the HI assay.

And I've showed a couple of pictures of where in the hemagglutinin model these particular changes are happening. So S145, on the left, you can see an antigenic site A. The 189, an antigenic site B at the top. And 158 is also an antigenic site B, also at the top, but on the right. So these are in addition to the two changes shared in the J.2 viruses, already discussed. If we go to the next slide, we can look at an actual HI assay, produced by the Francis Crick Institute, showing those reductions with the ferret antisera raised to the egg-grown Massachusetts or the egg-grown Thailand. And it's really when we see reductions, are when you see these additional

substitutions at the positions I mentioned, 145, 158, 189, or in combination. The majority of J.2s that don't have these additional substitutions were well-covered by the ferret antisera. We're also showing ferret antisera to a reference virus, Croatia/10136/RV/2023, which represents a J.2 that has an additional change at 145N. And ferret antisera raised to both the cell and the egg of Croatia shows better reactivity with the majority of the J.2s tested, as well as those with the additional substitutions I mentioned. And we can see that more in the antigenic cartography, which we'll go to next. Next slide, please.

Okay, so here's antigenic cartography from the Collaborating Center in London, at the Crick, on the left, and Australia Collaborating Center in Melbourne on the right. And this has helped showing what we're seeing with our HI assays, that the viruses in the J.1 and the base J's are actually closely related to each other in the map. So, they are in the light cyan, or blue, and purple. And these viruses cluster closely with the Massachusetts/18-like and the Thailand/8-like vaccine viruses. But you can see that viruses in the pink and the light purple have a couple of different patterns. The pink, you can see an initial cluster that are very closely related to the J viruses, J.1s and just J's. But there are a lot of pink viruses that are quite dispersed, and outside of the antigenic relatedness to these viruses. And for the light lilac, which represents J.4s, we're also seeing several of these be quite antigenically distinct. And again, when we look at these, we're actually seeing that there's a drift in the J.2s away from the base J's. And when we look at the outliers that have the most distinct location in the maps, these are the viruses with those additional substitutions of 158 or 189, in combination sometimes with 145. Next, I'm going to keep the map that's on the left from London, and I'm going to show serum circles showing where the serum has the greatest reduction. So, the next slide, please.

So these are two different serum circles. On the left shows the current vaccine virus, Massachusetts/18. And again, demonstrates that many of the J.2s are at the very edge of what we consider to be good reactivity with this ferret antisera. So the serum circle represents where an eightfold reduction would be. So, anything outside of that is greater than eightfold. And anything on the inside is just eightfold. So many of the J.2s and nearly all of the J.4s are falling outside of the serum circle for Massachusetts/18. We're seeing an improvement of coverage when we update the ferret antisera to that representative Croatia/10136/RV virus, which is that J.2 with the 145N substitution. So, here's where we're trying to understand the ferret antisera telling us that there is an antigenic drift in the J.2s and the J.4s, and then trying to understand, now that we have a subset of viruses that we've identified that have additional amino acid changes on the surface proteins.

The next question will be with post-vaccination human sera, does it look similar to the data that we've seen with our ferret antisera? So, and the next slide, please. So here are, again, results from multiple collaborating centers in the central regulatory labs of post-vaccination human sera, to the 2024 Southern Hemisphere vaccine, that includes the Massachusetts/18/2022-like and Thailand/8/2022-like vaccine viruses. We're looking for the GMT ratios compared to the cell Massachusetts/18. And as mentioned before, those in blue continue to show good reactivity and recognition of the viruses. And so, we can see that viruses that are just 2A3A1s, or in the J sub-plane, represent the vaccine viruses, and had good robust titers and good geometric mean ratios, compared to the vaccine viruses. However, when we look at representatives from the J.1, J.2 and the J.4 sub-planes, with additional substitutions, we're starting to see significant reductions with the human post-vaccination sera. And again, calling out specifically the conversion evolution that we're seeing at position 145, actually in several of the J subclades, and

then in particular in J.2 when we see changes at 189 and 158. And also changes at 189 in the J.4. So, our post-vaccination human sera is also showing reductions against the more recent and more evolved viruses that are circulating. Next slide, please.

This is a summary of the antiviral susceptibility. When looking at over 3,000 H3N2s, only one showed genotypic or phenotypic evidence of reduced inhibition to neuromodase inhibitors. For endonuclease inhibitors, 11 showed genetic or phenotypic evidence of reduced susceptibility to the endonuclease inhibitor baloxavir marboxil. Next slide, please. So, looking at the global circulation and the HA diversity, we continue to see significant H3 activity in Central and South America, Northern and Western Africa, Southeast Asia, and Oceania transition zones, during the Southern Hemisphere. Looking at the genetics of the viruses which circulated, while we're seeing just a small number of 2A3As, the vast majority are 2A3A1, and we look within 2A3A1 to see circulation of subclades J1 to J4. The J2 viruses predominate in most regions, although we are still seeing some J1s. And then when we look at within the J diversity, we're continuing to see several positions showing convergent evolution, and emerging subclades with changes at positions 145, 158, and 189, or in combination. However, in general, the majority of J2s did not have these additional substitutions, and we're not seeing an increase in viruses that have the changes at positions 158 or 189, to significant levels. Next slide, please.

So, using our antigenic characterization data, our post-infection ferret antisera started to show reduced to poor recognition of the J.2 subclade, again, highlighting additional substitutions where there was poor recognition. And similarly, the same substitution was also seen, K189 in the J.4 viruses. And when we look, we can see improved recognition when a reference virus to the J.2, with the S145N virus is used. Next slide, please. Looking at post-vaccination GMTs, we saw significant reduction for many of the circulating H3N2 viruses, again, when they were the

J.2 or the J.1, or the J.4 that had those additional substitutions at the positions mentioned. And that was seen across all serum panels tested. So, together, this data supported recommending that the District of Columbia/27/2023-like or the Croatia/10136/RV/2023-like, as the vaccine antigens for the 2025 Southern Hemisphere.

Okay. Moving on to influenza B. Next slide, please. And move ahead one more. Looking at global circulation patterns of influenza B viruses, as I showed in March, this actually has three colors in it, the orange being those for total influenza B detections, and then a subset, which is gone under lineage determination, in turquoise, showing B/Victoria, and in light blue, B/Yamagata. And the light blue actually goes right on the X-axis, so it's a little bit difficult to see. But, as mentioned previously, there has been no confirmed B/Yamagata detections after March, 2020. So, what we're really seeing in terms of epidemics for influenza B is due to the B/Victoria lineage, and which is true also for this reporting period. Next slide, please. And as I mentioned previously, influenza B viruses were detected more after February 2024. This is particularly true in China and other parts of Southeast Asia. And while all countries detected influenza B, there were really rarer proportions than the influenza A that was also co-circulating at the time. Next slide, please. Just a quick summary for B/Yamagata viruses in the next slide. Just repeating that there have been no confirmed detections of circulating B/Yamagata viruses after March, 2020. And again, the opinion of the WHO Vaccine Composition Advisory Committee is that the B/Yamagata antigen should be excluded. However, where quadrivalent vaccines are still used, the vaccine recommendation remains unchanged, as a B/Phuket/3073-2013-like B/Yamagata lineage virus. Now moving on to the B/Victorias in the next slide.

We can move forward one more. So, this phylogeography of the B/Victoria HA shows that since 2023, we've continued to see viruses that are part of the triple dilution plate,

particularly the V1A3A2. These 3A2 viruses share changes of positions 127, 144, and 203. And of course, we've split these up into subclades. And in particular, subclade C.5 represents viruses with an additional change in the hemagglutinin, at position 197. And it's really the predominance of the C.5 subclades since February of 2024 that we've seen. In particular, C.5.6, C.5.7, and C.5.1. And we'll move to the next slide to look at the geographic distribution. And here's where it's a little bit difficult to see, because there's so many colors. But there was a little difference. If we look at just the February, on the right, we can see that in the Americas, again, we're seeing a little bit of a different pattern of which subclade predominated. This was mainly the C.5.1s, whereas the majority of the regions detected more C.5.6 and C.5.7s. Okay, next slide, please. This summarizes the total antigenic characterized during this reporting period, and to previous reporting period. And as you can see, many viruses were tested. Okay, next slide, please.

So, the summary of the antigenic analysis using HI, for B/Victoria viruses, by the collaborating centers. As I mentioned, a good number of viruses for B/Victoria were analyzed, and extremely few showed reductions greater than eightfold in HI titers, compared to both the cell-grown and egg-grown B/Austria/135/94/17/2021-like vaccine-referenced viruses from the B1A, 3A2 subclade. Next slide, please. So doing due diligence, looking at the major clades that I mentioned co-circulated, our integrated phylogeography, genetic analysis, and antigenic analysis from CDC shows that, of the different C.5. subclades that were tested, there were actually none that showed greater than eightfold reduction to the ferret antisera, to the cell-grown B/Austria virus. So, although we're seeing some changes in the hemagglutinin, we have not seen antigenic drift associated with any of these particular HA changes. Next slide.

And this just summarizes cartography, showing in different colors, the different C.5 subclades, and how they cluster close together and close to the B/Austria ferret antisera. Across

multiple labs, so you can see that this is reproducible with different viruses and in different laboratories. Next slide. And then our post-vaccination sera to B/Victoria viruses. Here, the analysis shows that the current vaccine antigens of B/Austria elicited antibodies that well inhibited the majority of recent representative B/Victoria lineage viruses, across those multiple subclades, with additional substitutions in the HA that were observed. So we're seeing good recognition with post-vaccination human sera. Next slide, please.

Okay, summarizing antivirus susceptibility for B/Victoria. Over 2000 B/Victoria viruses analyzed, six showed evidence of reduced or highly reduced inhibition to neuromodase inhibitors. And when looking at endonuclease inhibitors, none showed evidence of reduced susceptibility to baloxavir. Next slide.

So, as a summary for influenza Bs, only B/Victoria lineage viruses were available for analysis. And although B/Victoria circulated globally, detections were lower than those for influenza A in almost all regions. In our genetics, we're seeing that only 3A2 HA clade viruses circulated. And we're seeing the predominance of clades that have the D197E substitution, but regional differences in which subclade predominated. Next slide, please.

For antigenic characterization, our post-infection ferret antisera showed ferret antisera raised against the vaccine viruses, well inhibited the genetic diversity of the 3A2 viruses tested. And in post-vaccination analysis of human sera, we're showing GMTs were not significantly reduced against most recently B/Victoria viruses tested. So together, this data supported the B/Austria-like viruses remaining as the vaccine antigen recommended for the 2025 Southern Hemisphere vaccine. So this concludes my talk, and I hope now that I have left enough time for questions.

Dr. El Sahly: Thank you, Dr. Kondor. That was very informative and thorough. I'd like to invite my committee colleagues to use the raise hand function so I see who has a question for Dr. Kondor. And we begin with Dr. Wharton, please unmute and put the camera on. Dr. Wharton.

CDC: Global Seasonal Influenza Virus Surveillance and Characterization – Q & A

Dr. Wharton: Thank you, Dr. El Sahly. So, Dr. Kondor, that was an amazing walkthrough, very clearly presented, enormous amount of information. And I'm always so impressed by the work that the global community does to help us have the best possible influenza vaccines for the upcoming season. You provided a tremendous amount of information about the evolution of the hemagglutinin components, of the H1 component, the H3 component, and the B/Victoria component, but didn't really present, unless I missed it, really anything about the neuraminidase component of those viruses. What role does evolution of the neuraminidase component play in the analysis of these data, and the recommendations that WHO makes for strain selection? Thank you.

Dr. Kondor: Thank you, Dr. Wharton. That was very nice, compliments. And we'll take that back to our staff. Yes, so looking at the neuraminidase, actually the analysis that's done on the genetic evolution is looking at the whole genome, although I didn't have time to go through that today. But what we look for with the HA and the NA, in particular, since they are the surface proteins, we're looking for coevolution and changes in circulation when an HA with particular changes may have a change in which neuraminidase actually includes. And we're talking about very minor changes. We actually break up the neuraminidase gene into clades and subclades as well. And so we look for which HA subclade has which subclade in its neuraminidase, and look at the particular changes in the neuraminidase protein, to see whether or not there's anything significant in known antigenic sites. In terms of antigenic evolution, what I've shown here, the

HI assay and the virus neutralization data shown, focuses on the HA antigenic evolution, because that is the primary antibody in the vaccine, but also that these assays assess. We have done, in the past, antigenic analysis for neuraminidase using the ELLA assay. However, that wasn't presented during this particular vaccine consultation. As, again, the primary antibody in post-vaccination human serum targets the human glutenin. And so this was the reason for why I only presented data for the antigenic evolution for HA.

Dr. Wharton: Thank you.

Dr. El Sahly: Thank you. You know, we hope one day we will be discussing a bit more than the HA, but we're not there yet. It has to do basically with the vaccine compositions. I have a clarification and a question. The clarification pertains to the post-human infection sera, for the H3N2 slide. I don't know if you can go back to it. I want to make sure I understood what you were trying to say correctly.

Dr. Kondor: It's slide 35, in what I presented, if that can help get back to that.

Dr. El Sahly: Yes, thank you. Here it is. Okay, so it looks like vaccination with the Massachusetts and Victoria, is it? Massachusetts and Thailand. Even with the J1, we're beginning to see dark orange, right? And my understanding, well, I can't see the exact number on all of them, but the darker the color, the higher the full change or distance from the vaccine. So, it appears that-- should a J2, J4 predominate in our part of the world, the Northern hemisphere? There may be quite a bit of antigenic distance, given the choice of the vaccine. So did I read that correctly?

Dr. Kondor: Right, and so this analysis is actually specifically looking at the geometric mean titer ratios, and not necessarily the total titer values.

Dr. El Sahly: Okay.

Dr. Kondor: If you zoomed in closely, you could see the actual titer values, for against the vaccine antigen, were quite robust. So we're seeing good geometric mean titers for those that be selected to have good titers against the vaccine. What we're seeing is that ratio. So, we're seeing a greater than 50% reduction across many of the viruses tested. And you're right, additional viruses in the J.1 and the J.4 also showed potentially significant reductions in that ratio. About overall absolute titers, you can see a little bit closer if you zoom in, but we did see robust titers, just it's the ratio of the titers. So, that suggests that although we can't predict today what viruses will circulate, not only in the Southern hemisphere for 2025, but for the Northern hemisphere that we're currently just beginning, we will be reassessing this as we go forward through the Northern hemisphere. to see post-vaccination human sera from Northern hemisphere campaign and in the Northern hemisphere population, how their results with the similar set of viruses would be.

Dr. El Sahly: Okay, thank you for clarifying. So, I understood this relatively correctly. The question I have, did we see J2, J4 circulate towards the end of our season here? Not just here, the Northern hemisphere in general.

Dr. Kondor: Yeah, the Northern hemisphere in general saw both J.1 and J.2 in most regions. J.3 and J.4 were in lower proportions, and regionally J.4 was mainly seen in Africa, as well as viruses outside of the J subclade in the 2A, 3A clades.

Dr. El Sahly: Okay, interesting story to follow. Dr. Monto, you have your hand, please unmute.

Dr. Monto: Yep, Becky, as usual, a very clear presentation of complicated data. In many years, the Southern hemisphere changes predict what's going to be in the next Northern hemisphere vaccine. So it's very nice to see that we don't have the usual problems in selecting an

H3N2 virus, specific virus, even though there is a worrying genetic diversity. My question is, whether I understood you properly, about the B, where there doesn't seem to be any problem in terms of the ferret sera. Was the VE lower for the B viruses? And if so, why?

Dr. Kondor: Yeah, I'll have to go back and review. I don't have it at the top of my head what the VE was for the B.

Dr. Monto: I thought you mentioned it. Maybe I misunderstood what you said, because B is usually pretty good in terms of VE.

Dr. Kondor: No, I think I was talking more about detections. So, if you look at the U.S. season and other seasons, you tend to see influenza A earlier in the season, followed by a later--

Dr. Monto: Yeah, we had a full-- B started, practically started the season this year.

Dr. Kondor: Yes, but had higher proportions post-January.

Dr. Monto: Thank you.

Dr. Kondor: And that’s true in some countries, especially also seen in parts of China, that actually had a pretty large B season as well.

Dr. Monto: Right. Thank you.

Dr. El Sahly: Great. Dr. Bernstein, please unmute and turn camera on.

Dr. Bernstein: Yeah. Hi, Dr. Kondor. That was, as the others have said, an impressive and clear presentation of complex data for me. I think I have a simple question, but I'm not sure the answer. When you showed some of the slides, you showed that the B lineage undetermined, that group was rather large. How do you define that? Does that mean it was tested for Victoria and

tested for Yamagata? And still couldn't be determined, or not? Because that segment was rather large in this particular year.

Dr. Kondor: Yes, that's a great question. That gives me an opportunity to talk a little bit about the types of surveillance information that's reported to WHO, that make these figures. The FluNet data can be reported from both sentinel and non-sentinel sources. So I'll use the U.S. as an example. Our non-sentinel sources include any clinical laboratories that we have. And in most clinical laboratory assays, they only detect Flu A or Flu B. So that's the result of that assay. It's only in our public health laboratories, that have the CDC B genotypes assay, that do the determination of lineage, of B Victoria or B Yamagata. Since the B lineage isn't necessary to have treatment options, that's why most clinical laboratory assays only detect the type. And so what you're seeing is a mixture of sources globally, where depending on the country that's testing and what source of their testing, they may only have an influenza A or B assay, and that's what they're reporting. Or, as what's provided to all GISHRS National Influenza Centers, they have our CDC lineage assay. And so, they're doing sentinel surveillance, which is a subset of all viruses that are circulating, where they're running the B lineage assay to determine the ratio and detection of B/Yamagata versus B/Victoria. And in all cases where our National Influenza Centers have run that assay, they've only detected B/Victoria.

Dr. Bernstein: So the likelihood is that these are all Victoria, not Yamagata?

Dr. Kondor: Very, yes, correct.

Dr. Bernstein: Thank you.

Dr. El Sahly: Thank you. I have a clarifying question, pertaining actually to the neuraminidase susceptibility. You indicated that, for the H1N1, there were 66 cases of reduced susceptibility,

versus zero for H3N2. The denominator is almost the same. Was this like a small outbreak, or more sporadic? Like was it a regional outbreak situation, or?

Dr. Kondor: Yes. So there were actually a couple of different factors in that. There was circulation during the Northern hemisphere, of particular genetic changes in the neuraminidase, that led to reduced susceptibility. There were two particular subclades that had changes that were noticed. However, these viruses haven't really circulated since May of 2024. And then throughout H1N1's history, individuals that have undergone oseltamivir treatment, and then tested, could tend to see a particular substitution at position 275 of the neuraminidase. This is a known mutation that confers reduced susceptibility to oseltamivir. And we're continuing to detect that. And when we look at these cases, we first identify whether or not they're treated, and it's a mixture of information. So, some were treated, some were not. And then we do ask the question, do we see community spread? Are we seeing a genetic association, in the HA and the NA, of these viruses? And these were pretty much sporadically detected. So there wasn't a circulating subclade that had that particular H275 substitution in the neuraminidase, in the data this season. And for N2, there have a couple of different markers that it tends to have, in terms of reduced susceptibility. However, those were not observed during this time period.

Dr. El Sahly: Thank you, Dr. Kondor. Any additional questions? I do not see raised hands. Going once, going twice. Alright. Well, thank you so much.

Dr. Kondor: It was my pleasure.

Dr. El Sahly: So, next on the agenda is the break. We are anchored by the open public hearing session. The open public hearing session is 9:55 a.m. Eastern. So we will reconvene then.

Ms. Hayes: Dr. El Sahly, we actually don't have registered speakers. So, if we want to stay ahead of schedule, we're open to starting after 10 minutes. It's up to you.

Dr. El Sahly: Oh, okay, I thought we had to. Alright.

Ms. Hayes: If we have registered speakers, that's correct. Yep.

Dr. El Sahly: Okay, so let's go with 10 minutes, then. Ten minutes will put us at 9:40. Let's go with 9:40 Eastern time. Thank you.

Open Public Hearing

Dr. El Sahly: Thank you. Well, welcome back, everyone. At the moment is the time for the open public hearing. However, due to no open public hearing requests received, this will end the open public hearing session. Next on the agenda is the discussion, recommendation, and voting.

Committee Discussion, Recommendations, and Voting

What I would like to do right now is invite my committee colleagues to raise the hand function in the chat in case you have a question or a comment pertaining to the topic one. I believe our colleagues from the CDC remain on the line to answer the question, right, Dr. Kondor?

Dr. Kondor: Yes, still here.

Dr. El Sahly: And the leadership of the FDA as well, of course. And the first question comes from Dr. Rubin. Dr. Rubin.

Dr. Rubin: Hi. Hi, thank you, Dr. El Sahly. And this gives me a chance to also compliment you on the great presentation, Dr. Kondor.

This is a slightly left field question, but for anyone who wants to offer an answer, is there anything we can learn from the disappearance of B/Yamagata? And is there anything we can

learn about perhaps pushing the evolution of viral strains to the point of extinction by causing fitness defects?

Dr. Kondor: All right. Thank you for the comment and for the question. So that's a great question about what can we learn from B/Yamagata changes, right, extinction. We're still trying to understand all the mechanisms responsible for the decrease in circulation. As we've looked at, you know, there's been significant antigenic changes that were occurring on the B/Victoria side and as well as a continued high level of population immunity to B/Yamagata. Prevent purposely actually also in the older population and the elderly. So we're seeing, you know, looking at our population immunity data, we're seeing high levels of antibodies against the B/Yamagata which circulated pre-2020.

And we also saw significant epidemics that actually had different age stratifications than normal. Normally B/Yamagata, B/Victoria, mainly seen in the very young children. But there were a couple of seasons where the elderly actually had pretty high levels of B/Yamagata. So we think a lot of it has to do with, you know, a robust population immunity to B/Yamagata. And then some type of fitness advantage with really antigenically distinct Victorias.

And then later on that, the mitigation strategies and change in basically person-to-person contacts and use of masking and shutdowns that could lead to really an extinction of something that had very, you know, very few potential, so that's all populations and really mainly being very, very young children. So I think this gives us hope for future vaccine platforms and strategies that really do create a strong and robust immunity. And I think you're right in terms of what we'll learn from this more is the interplay in fitness advantages when we have two distinct viruses circulating in potentially the same quote-unquote subtype where you might see something that was more genetically and antigenically divergent. So that three amino acid

mutation that we're seeing in the hemagglutinin and the Victoria have that fitness advantage. And so while I don't have all the answers today, I think this is definitely an area of active research going forward. Thank you.

Dr. Rubin: Thank you.

Dr. El Sahly: Thank you. So out of curiosity, how does that compare to the disappearance of the H2N2, for example.

Dr. Kondor: Yeah, I think what, you know, as we've seen with successful pandemics, there has been a decrease and an extinction of a previous subtype or in the case of H1N1 in 2009, a decrease in the seasonal H1N1 that preceded. So there is something to say that, you know, a mixture of level of population immunity and septal population with something new and really antigenically divergent can lead to an extinction. I think we're still learning more about the stem-related antibodies and how that can also help population immunity to specific hemagglutinins, such as we potentially could have seen with the H2N2.

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

Dr. Perlman: Yes. So, first, I also want to congratulate you on a great talk. I have a question about -- a little bit about the future. So there's a lot more discussion about adding the neuraminidase to the vaccine. And so much of this -- many of the studies that you're describing describe the loss of the catalytic activity, more of the neuraminidase than its antigenic determinants. Are you guys set up well so that if it is put in a vaccine that you can know what to look for in terms of drift or evasion?

Dr. Kondor: I think that is where there needs to be more additional active assay development. The current ELLA assay is difficult for many labs to run and potentially has a huge impact on which HA is, you know, is part of the virus that's used in that assay. So I think that is active area

Okay. So we have -- this is for question one, topic one. Dr. Portnoy voted yes. Dr. Offit voted yes. Dr. Berger voted yes. Dr. El-Sahly voted yes. Dr. Wharton voted yes. Dr. Rubin voted yes. Dr. Perlman voted yes. Dr. Bernstein voted yes. Dr. Chatterjee voted yes. Dr. Monto voted yes. And Dr. Gans voted yes.

Thank you. So that is for question one. And we will do this process one more time for question two. So if we could pull up the question two slide for Dr. El Sahly to read aloud for the record.

Dr. El Sahly: Voting question number two: For Quadrivalent 2025 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.

Ms. Hayes: Thank you, Dr. El Sahly.

And, again, for all non-voting members, please don't log out. We will be back in just a moment.

Ms. Hayes: Okay. So for voting question number two in topic one for today's meeting, out of the 11 total votes, we have 11 yes votes and zero no votes. So this voting question, just like the previous one, passes unanimously. And we can pull up the individual votes and I will read those aloud for the record.

Dr. Portnoy voted yes. Dr. Offit voted yes. Dr. Berger voted yes. Dr. El Sahly voted yes. Dr. Wharton voted yes. Dr. Rubin voted yes. Dr. Perlman voted yes. Dr. Bernstein voted yes. Dr. Chatterjee voted yes. Dr. Monto voted yes. And Dr. Gans voted yes.

So thank you for submitting all the votes. I will hand the meeting back over to Dr. El Sahly for any further vote explanations needed.

Dr. El Sahly: Yes. Thank you, Kathleen. So now, I'm going to call on my colleagues by name, just so they have an opportunity to comment on the vote today. And should you have no comments, that's okay, too. Just indicate so for the record.

I'll begin with myself. I voted such because of the presented data, especially with the change in the H3N2, which seems to be needed to expand the breadth of the immunogenicity in the population for what seems to be emerging drifts in the H3N2 strain. Of course, B/Yamagata is no longer circulating anywhere. At least there's no evidence of it, going on year three or four by now. But for manufacturing/regulatory reasons, phasing it out is taking a bit of time outside the United States, but looks like we will get there soon. And now, I will be calling by name, beginning with Dr. Gans.

Dr. Gans: Thank you, Hana. It was wonderful to hear the really robust collaborations that we have globally, and we're very lucky to be able to see this data and have such participation. So I felt very comfortable with voting the way that we did. And as Dr. Wharton had said, I think it's wonderful that we actually have options that we are able to select to really try and optimize our vaccines for the 25-26 season. I think what I'm hopeful for, and what I heard some suggestion of, is that there is continuing to be some innovation within the vaccine development sphere to figure out how we can really further optimize our vaccine efficacy. And so I look forward to that.

I would agree with you that I was glad to see in the WHO paper that there is still a recommendation to, as quickly as possible, and we know how the manufacturing limitations that we reviewed the last time limit the ability of some of these vaccines to take out the Yamagata, but I think that having it available for those areas so that people can be vaccinated against circulating strains is still very important. So that's why I voted the way I did.

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

Dr. Monto: I didn't ask Dr. Weir a question, which I will now because I have the chance. And that is, how long are the regulators in some of the countries in the world going to take to remove B/Yamagata? Because there are certain theoretical issues about continuing its use, which is the reason we try to get it out as soon as possible in the U.S.

Dr. Weir: Hi, Dr. Monto. I think the answer is it varies, apparently quite a lot, by regulatory bodies, and so I don't know how fast. I have heard that it's probably at least another year, if not maybe more, before all regulatory agencies around the world make this happen for all manufacturers.

Dr. Monto: And is there any way this can be pushed? Because there certainly was a push to get it out in the U.S.

Dr. Weir: Yeah. Well, I don't think the FDA can push it --

Dr. Monto: -- no, I don't mean the FDA. I mean other agencies, because it seems -- it seems a waste of resources to be producing a vaccine for a virus that doesn't exist anymore.

Dr. Weir: I couldn't agree with you more. I do think the WHO has been very strong. They repeat their statement every year, every six months, that it should be removed and there's no need for it. So I'm not sure what else they can do either.

Dr. Monto: Well, I guess it's up to the manufacturers to stop making it and force the issue.

Dr. Weir: Okay. You might want to get the manufacturers to comment on that.

Dr. Monto: Yes.

Dr. Weir: They are regulated in all of these different parts of the world.

Dr. Monto: Yes.

Dr. Weir: It's an ongoing problem.

Dr. Monto: Thank you.

Dr. El Sahly: Dr. Chatterjee?

Dr. Chatterjee: Yes. I voted yes on both questions based on the data that were presented by Dr. Kondor and concur with your comments, Dr. El Sahly, and also Dr. Gans' comments.

Dr. El Sahly: Thank you. Dr. Bernstein?

Dr. Bernstein: Thank you. I think the data suggests this is an appropriate direction to go, and I really don't have anything to add.

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

Dr. Perlman: Yes. So I agree with the votes and don't have much to add. I would just want to say one thing, which is I hope we get to a point that we can explain vaccine efficacy better to the general public. Because the numbers seem relatively low, but it's on a background of people having high immunity to the virus. So if we were compared to naive populations, the efficacy would be far superior, and there would be less people objecting to getting vaccinated.

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

Dr. Rubin: No add.

No, did you get me? Sorry, nothing to add.

Dr. El Sahly: Nothing to add. Okay, thank you. Dr. Wharton?

Dr. Wharton: Thank you. So I made my statement before the vote, but I guess I will add that I think this really does highlight the importance of our global surveillance infrastructure for influenza that provides the information that allows these decisions to be made, both by WHO and by the national regulatory authorities. And I would like to second Dr. Perlman's comment about how we talk about vaccine efficacy. I do think that I've learned some things about how to think about vaccine efficacy from our discussions about COVID vaccines, where we've gone from

incredibly high efficacy in a naive population to smaller increments of relative efficacy in a largely immune population. And I think we see the same thing every year with influenza. So I would totally second Dr. Perlman's comments. Thank you all very much.

Dr. El Sahly: Thank you. Dr. Offit?

Dr. Offit: Yes, thank you. I'm not sure I have much to add, other than my amazement, that we actually eliminated this B/Yamagata. I mean, you know, the short incubation period mucosal infections like RSV or influenza, rotavirus, SARS-CoV-2, human coronaviruses, I just never imagined we can eliminate those sorts of things. I'm not sure it has anything to do with what we did. I think it's more likely that it was out-competed, but it's an interesting story. And I liked Dr. Rubin's question, trying to figure out what we can learn from this. I'm not sure what we did other than maybe another virus competed it out. But thank you.

Dr. El Sahly: Yeah, I agree with you. I'm not going to take credit for eliminating it, though I'm happy for it.

Dr. Portnoy?

Dr. Portnoy: Yes, I agree with what's been said before. I would say that although the virus may have been out-competed, there are other examples of viruses that were vaccines, were able to make them stop circulating, such as smallpox. So vaccines can be used to make viruses stop circulating. In this case, we don't know if that's what it was, but it's a possibility.

I also want to compliment the fact that the information presented this time was so precise and concise that it didn't take very long to go through it. I thought it was presented a lot more clearly than it had been in previous sessions and didn't take as long, and it was a lot more understandable. So I really want to compliment the way that the information was presented at this meeting. I think it was really clear and very helpful in allowing us to make a decision.

Thank you.

Dr. El Sahly: Thank you. Dr. Berger?

DR. Dr. Berger: Thanks. I agree with all my colleagues here. The only thing I'll add is just that with Yamagata being removed, I would at some point like to see some discussion about whether there's potential benefit of adding a fourth strain, such as another A strain, that could incur greater coverage and protection overall. I agree with the concepts of not really producing vaccines that don't -- or include a component we know is not going to provide any benefit. But in this case, we potentially have the ability to swap in at some point. I understand regulatory issues of doing that, but I do think it's worth having a conversation at some point in the future. Thanks.

Dr. El Sahly: Thank you. So regulatory and the issue of immune imprinting has to be sorted out, especially with H3N2s, et cetera. I mean, it just can't be assumed that it can be added easily, but a lot of research needs to happen to answer this important question.

Well, thank you all. This wraps this part of the meeting. And this was supposed to have finished at 11:15, but we are finishing at 10:18. We had lunch scheduled on the agenda, but given how early it is, and it's only 9 my time, so I'm not going to have lunch now. So we will keep the agenda going and we'll have a lunch break after Dr. Oshansky's presentation from BARDA.

So, Kathleen, you want to announce the adjourning of topic one? The official adjourning?

Topic I adjourned

Ms. Hayes: Sure. Yes. Thank you, Dr. El Sahly. So thank you all, participants and speakers, for topic one of today's meeting. And topic one is officially adjourned. It's 10:20.

And we will move into – Dr. El Sahly, did you want to take a short break, even though

we're not doing lunch, before moving into topic two?

Dr. El Sahly: What does everyone want? I prefer to keep moving because the discussion was also rather short.

Ms. Hayes: Uh-huh.

Dr. El Sahly: Let's keep moving.

Ms. Hayes: Okay.

Topic II – Call to Order

Dr. El Sahly: So we hereby call to order the meeting pertaining to topic two. Topic two is to discuss pandemic preparedness for highly pathogenic avian influenza virus, including considerations for vaccine composition for H5 vaccines. I'd like to welcome all the members, the participants, and the public to topic two.

Now I will reintroduce Dr. Weir. Dr. Jerry Weir is Director of the Division of Viral Products at the Office of Vaccine Research and Review. Dr. Weir will introduce the highly pathogenic avian influenza virus vaccines for discussion.

Introduction to Highly Pathogenic Avian Influenza (H5) Virus Vaccines – Dr. Jerry Weir

Dr. Weir: Thank you, Dr. El Sahly. Welcome, everyone, again to topic two, which is our discussion of highly pathogenic avian influenza (H5) virus vaccines. I'm going to give you a brief introduction. Next slide.

First of all, the purpose of this discussion is kind of threefold. One, we want to update the VRBPAC, the committee, about the current influenza H5 situation in the United States, the status of currently licensed H5 vaccines, and a little update on ongoing clinical trials.

We also want to provide some clarification about the strain change process and the expected data requirements for updating licensed pandemic influenza vaccines during the inter-pandemic period, what we're in now.

And also, finally, to discuss with the committee the availability of H5 candidate vaccine strains that could be considered for incorporation into an updated licensed H5 vaccine. So if you go to the next slide, I've got a couple of slides to give a little background to how we got to where we are today.

As probably everyone knows, H5 and avian influenza have been a concern at least since the late '90s. In 2007, the FDA provided some guidance for approaches to facilitate licensure of pandemic influenza virus vaccines. This was in our Guidance for Industry entitled: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines. And we discussed in that guidance three different situations. One was for manufacturers of U.S. licensed seasonal influenza vaccines, and there we discussed that clinical immunogenicity studies would be needed to determine a dose and schedule for a pandemic vaccine. There was also a brief discussion in that guidance for manufacturers of U.S. licensed live attenuated vaccines, but we noted, as others had, that there are special concerns regarding clinical studies in the advance of a pandemic due to the possibility of re-assortment.

And, finally, we briefly touched on the situation for manufacturers without a U.S. licensed seasonal vaccines, and here we noted, as others had, the challenges in identifying immune surrogate to predicted clinical benefit for a vaccine which had not been shown to be efficacious for seasonal influenza.

Following that guidance, and in the same year in 2007, the FDA licensed the first H5 influenza virus vaccine from Sanofi Pasteur. This was two 90-microgram doses given intramuscularly 28 days apart for 18 to 64 years of age. Of note, the virus that was evaluated in this study was a Clade 1 H5A/Vietnam/1203/2004. Shortly after that, two years later, we did not have an H5 pandemic. We had an H1N1 pandemic.

In 2009, an H1N1 emergency was declared, and the agency, along with discussions with the VRBPAC, agreed that strain change supplements to their BLA, the license application, allowed the fastest availability of vaccine. Of note, though, clinical trials of these monovalent vaccines in 2009, these trials were initiated to confirm immunogenicity and also to inform any dose and schedule modifications that might be needed. Of course, there were none, which was good, but this data was submitted post-approval. Next slide.

A few years later, we had another in-depth discussion with the VRBPAC on the licensure of pandemic influenza vaccines and how one demonstrates effectiveness. In that discussion at the VRBPAC, we reiterated that licensure of pandemic influenza vaccines, in other words, for an influenza strain not included in the seasonal vaccine, these would be licensed as a new vaccine. Again, we reiterated that safety and immunogenicity data to select the dose and the dosing regimen would be required before licensure of a pandemic vaccine. But we made it clear that we would infer the effectiveness of these pandemic vaccines from the seasonal vaccine, assuming the seasonal vaccine had shown efficacy and the manufacturing process was the same.

The initial licensure of a pandemic vaccine under this scenario was considered as a prototype that would permit a future strain change supplement in the event of a pandemic. Of note, the committee also felt that it was premature, again, to discuss licensure of pandemic influenza vaccines that were not dependent on an HA antibody response.

A few years later, in 2013, we licensed the second H5 influenza vaccine. This one was adjuvanted, and it came from ID Biomedical Corporation of Quebec. And the dose were two 3.75-microgram doses with an ASO3 adjuvant, also given intramuscularly 21 days apart, 18 and older, and there was a half-dose version for six months to 17 years of age. The virus strain that was evaluated in these studies was a Clade 2.1.3.2 A/Indonesia/05/2005.

More recently, in 2020, we licensed the second adjuvanted, a third pandemic H5 vaccine, but a second adjuvanted H5 influenza vaccine. This one made in MDCK cells by Seqirus, and this one was two 7.5-microgram doses with an MS59 adjuvant, intramuscularly 21 days apart, six months and older. And the strain of virus that was evaluated in these studies was a Clade 2.2.1 A/turkey/Turkey/1/2005. Next slide.

This shows -- you saw this earlier, but this is essentially a schematic of the regulatory pathway that we have used over the last several years for licensure of pandemic influenza vaccines. This was the process used for all three of the vaccines that I just described. It also -- the scenario assumes that any strain changes recommended by VRBPAC would be implemented during a declared pandemic, but would not require clinical data prior to the approval. And so you see on the left in all the blue boxes, this referred to vaccine makers that had licensed seasonal influenza vaccines which had demonstrated efficacy. Their prototype pandemic vaccine would be subtype specific, and the licensure approach would include safety and immunogenicity data in advance of the strain change supplement, in advance of the licensure of the pandemic vaccine, and we would infer effectiveness from the effectiveness of the efficacy of the seasonal vaccine. During a pandemic, again, with the recommendation of the WHO and the VRBPAC, the pandemic vaccine could be updated with a strain change supplement fairly rapidly. Next slide.

I want to briefly go over some recent developments that sort of are the reason that we're here today. First of all, the H5 influenza viruses have continued to diversify genetically and antigenically into multiple clades and subclades, but in recent years, H5 virus isolates have been almost exclusively from clades 2.3.2.1 and 2.3.4.4. You'll hear more about this in the CDC presentation, but the point is that the viruses that were used, strains that were used in the prior

prototype vaccines are no longer circulating.

The other hand, highly pathogenic -- after an absence of several years, highly pathogenic avian influenza H5 viruses reentered North America and subsequently into the United States at the end of 2021 and early 2022. These viruses evolved rapidly and resulted in large outbreaks in wild aquatic birds, commercial poultry, marine mammals, and, of course, dairy cows, and there have been sporadic human infections also have been reported. You'll hear more about this also in the later presentations. Genetic analysis indicated that these H5 viruses circulating in the U.S. are from H5N1 clade and 2.3.4.4b, and that the hemagglutinin is closely related antigenically to the HA of a recent human H5N8 isolate, A/Astrakhan/3212/2020. Candidate vaccine viruses have been prepared for A/Astrakhan, as well as some more recent virus isolates of clade 2.3.4.4b such as A/American Widgeon/South Carolina. Again, you'll hear more about the candidate vaccine preparation in the later presentations.

But as a result of all of these developments, manufacturers have requested additional details and clarity about the process for updating strain composition of pandemic influenza vaccines in the inter-pandemic period. The next slide shows a schematic of -- next slide.

The next slide shows our proposed process for updating vaccine -- pandemic influenza vaccines in this inter-pandemic period. First of all, we want to continue to work with the VRBPAC with these recommendations, and so our proposal is that under -- depending on the circumstances, we will periodically discuss with the VRBPAC whether a change to the current composition of a licensed prototype vaccine is needed for preparedness purposes. At the same time, we would like to discuss with the committee the appropriateness of currently available candidate vaccine strains for a possible update to licensed prototype vaccines. The manufacturers of these licensed pandemic vaccines can then prepare a data package for regulatory review for an

updated pandemic vaccine, and this data would include, first of all, the chemistry, manufacturing, and control data for the updated vaccine to ensure product quality and consistency. And second, it would include clinical immunogenicity and safety data. The VRBPAC would be expected to reconvene if and when a pandemic really were to emerge and be declared and make a final composition recommendation. A schematic of this process is shown on the next slide.

You've seen this before, but this is our revised proposal. Again, in the pre-pandemic period, we would still license prototype vaccines based on the same manufacturing process for a seasonal vaccine that shows efficacy. We would infer effectiveness from the seasonal vaccine that had shown efficacy, but now in the inter-pandemic period, we would entertain updates to the licensed vaccine as supplemental BLA strain changes. Here we would ask for, as I just said, safety and immunogenicity data. We would continue to infer effectiveness based on the seasonal -- the efficacy in the seasonal influenza vaccine. But then, if and when a pandemic should occur, we would also update the supplemental BLA or the strain change if needed. In other words, if the already updated prototype matched what was circulating, then we would be already ready to go. But then again, depending on the way the virus evolves, it could yet again be another strain. But in any case, during the pandemic, we would use the strain change supplement and the safety, immunogenicity, and even effectiveness data would come post-approval. So, once again, for this process, we again assume continual VRBPAC input, but it's the timing of the supportive data submission that differs between an inter-pandemic and a pandemic situation update. Next slide.

Okay. So after you've heard the presentations from CDC and BARDA, then we would like the committee to discuss and provide input on the proposed strain change process during the

inter-pandemic period. Also, we would like you to discuss whether a change to the current composition of licensed prototype vaccines using the proposed process is needed for preparedness purposes, and whether the candidate vaccine viruses are available that are appropriate to update the current licensed prototype vaccines. I'll stop there and take questions before we go to the CDC and BARDA presentations. Over.

Introduction to Highly Pathogenic Avian Influenza (H5) Virus Vaccines – Q & A

Dr. El Sahly: Yes. So I invite my colleagues to use the raise your hand function.

I'll begin with a clarification point before we begin. So at the moment, of course, the H5N1 is the one that is most concerning. However, there are other strains for which we prepared vaccines, at least in terms of phase one, phase two clinical trials, like H7N9. So is it really a strain change or more like a strain addition, like, just to be ready for this particular, I guess, clade of concern?

Dr. Weir: So if I understand your question correctly, we have so far viewed these as subtype specific, and that is just simply based on the amount of data that we have. So if a manufacturer wanted an H7 vaccine, we would expect them to submit a licensed application for an H7 vaccine, and once again, provide the safety data, the immunogenicity data to inform the dose and the dosing regimen. And again, there's just still a limited amount of data done for other subtypes. There's a little bit for H7, practically none for things like H9, H10, and so we would still view these as subtype specific vaccines, at least to date.

Dr. El Sahly: Okay, thank you. I mean, there's a lot on H7, but yeah. Dr. Rubin.

Dr. Rubin: Thanks, Dr. Weir, and I want to salute the FDA for being, you know, being so proactive about this.

One thing that I didn't see in the algorithm is animal efficacy. Is that important to read out for flu vaccines? And how well does it correlate with responses in humans?

Dr. Weir: In general, for influenza vaccines, animal data hasn't been as important. I mean, as you know, for seasonal vaccines, and even for pandemic vaccines, we use animal data mostly to inform us about antigenic differences among viruses, but not to inform us much about efficacy or effectiveness. We rely on the immunogenicity in human studies to do that. Is that what you meant?

Dr. Rubin: And that was it. Thank you.

Dr. Weir: Okay.

Dr. El Sahly: Dr. Gans.

Dr. Gans: Thanks very much. I had a question since -- a couple of questions. Was the VRBPAC involved with all of the previous licensures, including the one in 2020? I only say I might have missed that meeting, but I don't recall that coming to the committee. That's my one question.

My second question, more importantly, is how quickly -- or what is the time gap between pandemic strain being identified and then being in that pandemic state that we want to get something to market? What is that time lag?

And then to just follow up on animal, slightly different question. Clearly we're dealing with human-specific vaccines, but are commercial birds and the cattle also being targeted, given that that's a huge, obviously, source for human infection? Obviously not the wild animals.

Dr. Weir: Okay, so I can answer some of it. First of all, the VRBPAC was consulted specifically for the first two H5 vaccines that were licensed. The third one in 2020, I'm pretty sure we did not have a VRBPAC session for that since it was essentially very similar in the terms of licensure to the one that preceded it. It was also an adjuvanted, so we'd already discussed with the committee the licensure of an adjuvanted H5 vaccine. We'd already, of course, discussed

with the committee licensure of Seqirus's MDCK vaccine, so we did not go to the committee for that particular one, but we had extensive discussions for the Sanofi and the IDB medical vaccines in the previous years. That was the first question.

The second one was about timing. So timing is hard to predict. I think we all, not just the FDA, but we're all doing everything we can to be as prepared as possible to shorten that -- the time needed to get a vaccine to market. And as you'll hear in the later presentations, we have -- besides the strain change process, which I think speeds things up, you will hear that there's already quite a bit of work going into clinical studies to evaluate these same vaccines, and I think the -- and pilot lots of these vaccines have already been made. So I think the time, if the virus that emerged was very similar in humans, was very similar to what we're talking about now, I think the response could be very fast.

On the other hand, with influenza, everything is unpredictable. I mean, I don't think anybody predicted the emergence of the 2009 pandemic. I know for sure that when we had the H7 emergence, the highly virulent emergence in 2013, that wasn't exactly on everybody's radar either. So obviously if it's something unexpected like that, the timing will be longer, but I think for H5, where -- everyone is doing everything they can to shorten that time as much as possible. The third question, I think, was about vaccines for animals. Was that right?

Dr. Gans: Yeah, I'm just wondering about the domestic.

Dr. Weir: Yeah, I actually don't know here. I think there are a lot of challenges to developing vaccines for both poultry and certainly for cattle, and I don't know how much studies have been done. I know that in some parts of the world, of course, vaccines are given for H5 and even H7 in domestic poultry, but that has never been the case in the U.S. And I don't know what the status is, and I don't know how many studies are being done to do that. I know logistically it's

fairly difficult, but it's not my area of expertise, I admit. Over.

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

Dr. Chatterjee: Yes. Thank you, Dr. El Sahly. Dr. Weir, my question is regarding the regulatory pathway for these influenza pandemic, potential pandemic viruses. So I was curious as to why we would use the licensure pathway as opposed to an emergency use authorization during a pandemic.

Dr. Weir: Okay. I'm sorry, I actually thought about mentioning that. If it were a pandemic, I'm sure we would use everything, including emergency use, but the emergency use would be for vaccines that were not already licensed. I think there is -- and we've always thought at the agency – that there was an advantage if one could have a vaccine that was licensed. I think that's important for the public, and I think we would certainly use that if possible, but you are right that if a pandemic emerged, we would consider other mechanisms, and we would -- I'm sure we would be using emergency use for other vaccines that had not gone through, that were not already licensed. So I think we would use everything in an emergency. Over.

Dr. Chatterjee: Thank you very much, Dr. Weir. Given how rapidly these viruses change, it is likely that in a pandemic we would see a different virus than what we would see in the inter-pandemic period.

Dr. Weir: I couldn't agree more that the unpredictiveness of influenza isn't always a challenge, yes.

Dr. El Sahly: Okay. No additional hands. Thank you so much, Dr. Weir.

Now I'd like to invite Dr. Todd Davis. Dr. Todd Davis will go over the Highly Pathogenic Avian Influenza A(H5Nx) virus surveillance and characterization in the U.S. and globally, and recommendations for candidate vaccine virus development. Dr. Todd Davis is

Acting Chief at the Virology, Surveillance, and Diagnosis Branch Influenza Division within the CDC. Dr. Davis?

CDC: Highly Pathogenic Avian Influenza A(H5Nx) Virus Surveillance and Characterization in the United States and Globally and Recommendations for Candidate Vaccine Virus Development – Dr. Todd Davis

DR. DAVIS: Terrific. Thanks for the introduction, and thanks very much for the opportunity to speak to all of you today. Next slide.

So just to give you a brief update on the plan for this presentation, I want to give an overview on the process that the WHO Global Influenza Program and the Global Influenza Surveillance and Response System, as well as the collaborating centers like the Influenza Division at CDC put into making recommendations for pre-pandemic candidate vaccine virus development and the testing that goes into that process. I'll also then move into discussing specifically the epidemiology regarding where we are in the U.S. in terms of H5 circulation, both in animals and human cases. And then also talk about specific data on the genetic and antigenic characterization of those H5 viruses that have been detected in the United States.

And then finally, talk specifically about the outcomes of the September 2024 WHO information meeting on antigenic and genetic characteristics of these candidate vaccine viruses. That's very much in line with what Dr. Kondor presented relative to the seasonal recommendations. Again, and I'll explain a little bit of that process and how the pre-pandemic selection is also very much a part of the VCM process. Next slide.

Of course this all starts with surveillance. So I'll also discuss just briefly to touch on how the surveillance that's set up within the United States that's used for seasonal influenza virus detection is also really the core of the surveillance that detects zoonotic cases as well, and this includes also the zoonotic cases of swine-origin influenza viruses that do sporadically occur in

the United States. So like the seasonal surveillance strategy, you know, viruses are collected from patients from hospitals and clinics around the country. Those are triaged to state and local public health laboratories. Like seasonal subtyping, the influenza division also develops diagnostic kits that also subtype H5 viruses, and these diagnostic kits are made available to all state public health laboratories across the United States. And once those viruses are identified, of course we do genetic analysis of the strains that are submitted not only to CDC, but also through some of our state public health laboratories that are actively involved in sequencing directly from clinical specimens. And then using the sequencing first strategy, again, sequencing from clinical specimens, we select viruses for phenotypic characterization.

Now, for the zoonotic viruses, nearly all of those that are able to be propagated in either cell culture or embryonated chicken eggs are characterized phenotypically, and we're able to do antigenic characterization as well as antiviral susceptibility testing. And then that further breaks down into a small subset of those viruses that have unique properties that make them different from previously recommended pre-pandemic candidate vaccine viruses, where we'll go into development of a new CVV, depending on that antigenic diversity that's seen in our phenotypic characterization. Next slide.

Besides the domestic surveillance, like the seasonal influenza surveillance, there is also a large network of international laboratories that's coordinated also through the GISRS network, and this includes national influenza centers that are found in more than 125 member states. Atlanta CDC, again, is a collaborating center. There are seven other collaborating centers that are also actively engaged in helping these national influenza centers to build testing capacity to triage specimens to collaborating centers so that we can do additional genetic and phenotypic characterization of viruses that are collected through this network of laboratories from all around

the world.

In addition to the national influenza centers and the collaborating centers, there are also WHO H5 reference laboratories. There are 12 of these. Atlanta CDC is also considered an H5 reference laboratory. And these laboratories also are able to conduct surveillance in animals as well so that we can collect data on the genetic and phenotypic characteristics, not only of viruses that are detected in humans, but of viruses that are also circulating in the animal host. Next slide.

In addition, as part of the vaccine consultation meeting, we also have members from these H5 reference laboratories that attend the VCM and share real-time data on the same timeline that the seasonal characterization is reported. So we work on a six-month timeline. Data is compiled and shared every six months, both in February and September during the VCM meetings, and includes this list of laboratories, again, that are H5 reference labs. And in addition to this, we also invite participants from the OFFLU network. So OFFLU is an acronym that combines the FAO as well as what was formerly the OIE that is now the World Organization for Animal Health. And their network of laboratories is also a fairly exhaustive list, which is shown here on the screen. These are all laboratories, primarily veterinary laboratories, that are also doing influenza surveillance in animal reservoirs. They compile all of their data also on that six-month reporting period timeline, and bring that information to the WHO VCM so that we can all look at the data together and, again, use that to analyze both the genetic and phenotypic data that goes into decisions on which pre-pandemic candidate vaccine viruses to recommend for development. Next slide.

In addition to this, the U.S. CDC is also able to fund our own surveillance activities and collaborate with other U.S. government agencies, including the U.S. Department of Agriculture that has quite a robust swine influenza surveillance program and is responsible for monitoring

outbreaks of avian influenza across the United States. There's close collaboration with the National Veterinary Services Laboratory so that we can analyze data that they are generating, as well as perform phenotypic testing of viruses that they're isolating through their animal surveillance programs.

We work closely with the Centers for Excellence for Influenza Research and Response, or the CEIRR network, supported by NIH, and then have several academic partners. I mentioned one here at The Ohio State University that's really integral in understanding circulation of swine influenza viruses, especially in agricultural fairs and swine exhibitions. And then, finally, we fund a number of different projects to look at the animal reservoir in countries where we believe there's a high risk for human exposure to avian and swine influenza viruses. Next slide.

Like Dr. Kondor presented, a lot of what we do on the zoonotic side of the candidate vaccine virus recommendations are based on the same principles. We look at the epidemiology, the clinical data. We look across the GISRS network and the virus surveillance that's conducted, again, across the laboratories that I just discussed. Genetic analysis is performed and we are able to isolate viruses that have unique genetic properties. We do antigenic characterization. This also includes immunizing ferrets with viruses to generate immune sera to those viruses. It gives us panels of ferri antisera that we can then use to understand the antigenic diversity that is found in these viruses, and this includes performing hemagglutination inhibition tests that assess the cross-reactivity of a new virus to sera that's generated against the HA protein of those viruses that the ferrets are immunized against. And we also do neutralization studies, which also looks at the ability of antibodies raised in ferrets to neutralize the replication capacity in an in vivo model and in vitro testing.

Part of this also includes looking at post-vaccination human serologic analysis, and so

using post-vaccine human sera, we do also have the luxury of being able to compare these viruses to human populations, oftentimes age-discriminated vaccine human sera that we're also able to look at the cross-reactivity of antibodies post-influenza vaccination to these zoonotic strains.

And then finally, this data is integrated through the VCM process. A lot of the data, of course, is also deposited to public sequence repositories so that we can all analyze each other's data in real time as well, and that goes into the final decisions on the new candidate vaccine virus recommendations. Next slide.

So like the seasonal influenza virus recommendations for the zoonotic candidate vaccine viruses, this is a primary goal of the WHO committee on the influenza vaccine composition. Again, we do this twice each year, both in February and September, to coincide with both the Southern and Northern Hemisphere seasonal vaccine recommendations. Our goal, perhaps one of the differences, is that we're looking for pre-pandemic candidate vaccine viruses that elicit the broadest immunity against an increasingly diverse population of zoonotic influenza viruses, and this is especially true for H5. I'll get into some of those details in a minute, but because these viruses evolve in discrete animal populations and in discrete populations of the world and are not transmitting among humans, we oftentimes see quite a lot of antigenic diversity. So we're not only recommending many, many pre-pandemic candidate vaccine viruses against all of the circulating clades of H5, for example, but we're also looking for those pre-pandemic candidate vaccine viruses that give us the largest breadth of immunity across the number of circulating strains. I'll talk a little bit about that more in detail.

And then, finally, just not to belabor this too much, a lot of the questions that we're asking, again, are very similar to the same questions that are asked for seasonal vaccine strain

selection, things like which genetic clades are circulating, where are they, how long have they been observed, what do the hemagglutinin proteins look like, are there specific amino acid changes in the hemagglutinin protein that would be predicted to lead to reduced cross-reactivity with vaccines or to ferret antisera raised to specific prototype viruses. We look at severity of human illness as a factor for consideration. We oftentimes focus our recommendations based on where we have seen human disease in the population rather than recommending CVVs only for those viruses that are circulating in animals. And so I'll go into some of those details next, specifically to focus on the H5 viruses. Next slide.

And finally, for the generation of the pre-pandemic CVVs, we use two different approaches. They're both based on reverse genetic technology, wherein we can clone the HA and NA into plasmids and then transfect those plasmids into cell culture to rescue the candidate vaccine virus. By cloning, we're able to remove the multibasic cleavage site that gives H5 viruses and H7 viruses their highly pathogenic phenotype in the chickens, and this is something that's a requirement for being able to use these viruses for manufacturing so that we're not creating a CVV that could be pathogenic in the avian host.

Then we're able to generate seed stocks, propagate those in eggs, and conduct additional testing. We also use synthetic gene approaches as well, especially when we don't have access to a specific wild type virus. We're able to use sequence data alone to synthesize the genes for both the hemagglutinin and the neuraminidase, again, removing the polybasic cleavage site from the hemagglutinin before those are then cloned into the HA and NA plasmids and transfected. Next slide.

Once we have our candidate vaccine virus rescued, again, we put this through egg propagation because we want to be sure that we're working with a candidate vaccine virus that

has high yield in embryonated chicken eggs, again, with the assumption that many of the vaccine manufacturers would be using an egg model for production of the vaccine. And that allows us then to generate what we classify as good laboratory practice, or GLP, vaccine seed strains that can be distributed to vaccine manufacturers. But before that distribution occurs, we go through a number of studies, testing that also allows us to be sure that these vaccines are of the highest quality and that they meet conditions for good laboratory practice so that they can be used for manufacturing. And this includes sequencing, performing exclusivity tests to make sure that we don't have any contamination in our seed stocks. That includes analyzing viruses and the seed strains for sterility to ensure that there's no bacterial contamination.

We perform a series of tests to be sure that these are also nonlethal to the avian host. We no longer perform chicken pathogenicity. This used to be required for select agent exclusion, but USDA, based on several decades worth of data, has allowed us now to circumvent that. We're now showing that the viruses are not lethal in the embryo and that they require trypsin-dependent replication. But we also do ferret safety testing, so we put these viruses into ferrets to be sure that they are safe and attenuated compared to the wild-type strain in the ferret model. And we generate ferret antisera so that we are also able to do HI testing or neutralization testing to demonstrate that the antigenicity of the vaccine is similar to that of the wild-type virus from which it was based.

And then, finally, we do stability testing to make sure that there's no genetic changes in these vaccine candidates by passaging 10 times in embryonated chicken eggs. And a lot of this, of course, is coordinated with other U.S. government agencies, as well as the World Health Organization, which I think Dr. Oshansky will talk about after my presentation. Next slide.

Ultimately, all of this information does go into publicly available information that's

posted on the WHO's website, so there's two links at the bottom of the slide that do show which candidate vaccine viruses have been developed over a number of many years, as well as the reagents that are available to do characterization of the candidate vaccine viruses. And then, again, every February and September, we also post online a report of the outcome of the six-month reporting period showing all of the genetic and antigenic data that's been compiled from those laboratories that are involved in the VCM process. Next slide.

Okay. Now I'm going to focus specifically on the highly pathogenic H5 viruses. I use the term NX, which I'll talk about in a little bit, because of the nature of these avian influenza viruses to frequently reassort. I'll go into some of those details in a minute. Next slide.

So this is a timeline just showing sort of the basic trajectory of how H5N1 viruses first emerged that occurred in 1996. At least, that was the first known detection of what we call the Goose/Guangdong/1/1996 lineage of the highly pathogenic H5N1 viruses that emerged in southern China. This virus then spread for many years across Asia, eventually into Europe and parts of Africa and the Middle East after some drastic expansion via migratory birds. People refer to this sometimes as the Qinghai Lake expansion that occurred around 2005. And because, again, of the geographic distribution of these viruses in discrete animal reservoirs, the virus began to evolve, so we started to develop a clade nomenclature system back in 2005 to be able to more easily communicate which viruses we were actually discussing among the scientific community. So this clade nomenclature system started with the Goose/Guangdong virus, which is clade zero, and has subsequently emerged into now more than 30 different genetically defined clades of the hemagglutinin protein. And so that's where that phylogenetic tree, where you start to see the diversity shown in 2005, is important.

So as the virus evolved in the HA, there were also a number of re-assortment events. So,

again, these viruses spread through migratory birds, and during that spread, migratory birds also carry other non-highly pathogenic viruses, so low-pathogenicity avian influenza viruses that contribute their genes to the Goose/Guangdong lineage of H5 strains.

And so in 2014-2016, what we used to know as H5N1 nearly ceased to exist, with the exception of a couple of pockets in certain parts of the world, and instead, the virus that was circulating among poultry in many parts of the world became an H5N6, because the neuraminidase was replaced with an N6 neuraminidase, and in other parts of the world, viruses were circulating that were an N8 subtype. So, for example, even in the U.S., the virus that did result in poultry outbreaks for about two years beginning in 2014 and ultimately disappeared, was primarily H5N8 viruses, although there were a few other neuraminidases that were detected as well. Those two subtypes continued to circulate throughout 2018 to 2020. There was further diversification among the HAs. I'll go into a bit more detail at the next slide. But ultimately, that led to where we are today.

So there was an additional re-assortment of a wild bird neuraminidase that returned these viruses to the H5N1 subtype, but the neuraminidase of the current H5N1 virus and the one that's currently circulating in dairy cattle, for example, actually has a different neuraminidase than the original neuraminidase that was found in the goose/Guangdong lineage virus. So I think that's an important point to remember, that these neuraminidases do reassort frequently, often in unpredictable ways because they're driven by re-assortment events that happen in the wild bird reservoir. So that again brings us to where we are today. Next slide.

And as such, because of that neuraminidase re-assortment, a lot of our efforts are focused on nomenclature surrounding the H5 surface protein. This is also the protein that elicits the immune response in the ferret model and gives us the tools that we are able to characterize the

viruses based on the cross-reactivity to the hemagglutinin.

But as I said, the HA has continued to evolve, and really, as of this year, we are now focused on three clades that remain in circulation in different parts of the world, the 2.3.4.4s, the 2.3.2.1as, which are limited primarily to India, Bangladesh, and Nepal, and the 2.3.2.1 viruses, which are primarily limited to some pockets in West Africa and the Mekong Delta region of Cambodia, Laos, and Vietnam. Next slide.

So the 2.3.4.4s. So the 2.3.4.4s began to evolve in the mid- to early-2010s, and as you can see, even among the 2.3.4.4 clade of these viruses, we now refer to these as fifth-order clades that include viruses that are classified as 2.3.4.4a through 2.3.4.4g. These viruses also have diversified into discrete corners of the world, with some of them only detected, for example, in China for the 2.3.4.4hs or for Indonesia for the 2.3.4.4es. But the 2.3.4.4bs are the ones that have really, I think, been the focus of most of our attention over the past couple of years. This is the virus that has circulated among wild birds in Africa, Asia, Europe, and the Americas, and that has now spilled over into dairy cattle and has continued to cause domestic poultry outbreaks, as well as spill over into other wild mammals.

The other thing I'll point out is that as part of that candidate vaccine virus recommendation, because we have seen these genetic groups emerge over the years, the WHO, and then through the VCM process, has recommended candidate vaccine viruses that represent the majority of these fifth-order clades of the 2.3.4.4 viruses, and if you look closely on the tree, you'll see those highlighted in red. Next slide.

But to hone in this a bit more, this shows a list of all of those 2.3.4.4 candidate vaccine viruses that have been recommended through the WHO pre-pandemic CVV recommendation process, and as I said, there have been recommendations and development of CVVs that

represent all of these different HA clades. So we now have CVVs that cover clades 2.3.4.4a through 2.3.4.4h, as shown in this table. Some of those are still pending completion because some of them have been de-prioritized because of the time it takes to produce the CVV, which is generally about an 8 to 12-week timeline in the best circumstances. Some of those have been de-prioritized where we focus specifically, for example, on the 2.3.4.4bs. Next slide.

And so for 2.3.4.4bs specifically, I wanted to get into some additional details, again, to kind of refocus our look at what is actually happening within the United States and the work that's going into the genetic and antigenic characterization of the 2.3.4.4b viruses. Next slide.

So if you look just at the fifth-order 2.3.4.4b viruses, because of the ongoing genetic diversity of these viruses, you can see that we can also break them down into discrete phylogenetic groups that also have some geographic clustering patterns. So we see some groups that are circulating only in Asia, some in Africa, some only in Europe and the Middle East, and now a cluster of viruses that has been detected in the Americas. And for each one of these discrete groups, there has also been genetic and antigenic characterization to recommend candidate vaccine viruses that cover each of these different clusters of viruses found in these different parts of the world, and those are shown in red text throughout the phylogenetic tree. Next slide.

And like the other list, this is now just a list focusing only on the 2.3.4.4b candidate vaccine viruses that have been developed. So a lot of the energy initially was focused on developing pre-pandemic candidate vaccine viruses that targeted the HA of the Astrakhan 2020 virus. This was a virus whose prototype strain was from a human case that occurred in the Russian Federation back in 2020, and one of the earliest signals that the 2.3.4.4bs were evolving in such a way that they were no longer being cross-protected by previously recommended

candidate vaccine viruses. So both the CDC as well as FDA focused our energies on developing candidate vaccine viruses to the Astrakhan strain. These were initially recommended by the WHO in February of 2021, and those candidate vaccine viruses were completed and available to manufacturers in January 2022 in the case of CDC and November 2021 by the FDA.

Two others have also been recommended, one from a poultry virus that's been circulating in West Africa that also has some unique properties which I'll talk about in a minute. It provides broad cross-reactivity against a number of viruses that are circulating across Europe and Africa, and this is a CVV that's being developed by CDC that is now pending completion. And as well, during the emergence of the H5N1 viruses in North America, there was also a recommendation to develop an American Widgeon/South Carolina CVV that the CDC has completed. That was recommended in February of 2023 and we completed the CVV development in September of 2023. I'll talk a bit more about all of these in a minute. Next slide.

So to level-set on where we are currently with the circulation of the 2.3.4.4b viruses, most of these that are shown here on this map, and this represents viruses that have been detected in wild birds and poultry and mammals across the world over the six-month reporting period beginning in February of 2024 through September of this year. So you can see that these 2.3.4.4b viruses circulate broadly. Everything in light blue represents H5N1 viruses, although there still are some other subtypes with different neuraminidases that are also detected in certain parts of the world. So as you can see, quite a large distribution of these viruses, and because of the dairy cow outbreak in the United States, of course, a large number of viruses that have also been detected in this current reporting period. Next slide.

This is a table showing the number of human infections that have been reported in the last six months. As I mentioned, there are other clades that are circulating. We know that the

2.3.2.1c viruses, for example, have caused severe and fatal disease in Cambodia and Vietnam. But again, to try and remain focused just on the 2.3.4.4bs, I just wanted to highlight that, you know, we continue to see a number of human cases in the United States. These are individuals with exposure to dairy cattle, and in the case of Colorado this year, individuals exposed to infected poultry. And then one case from Missouri, where there is still no epidemiological link to an animal host. And then I'll just add that in China as well, there was also one fatal case of 2.3.4.4b after a person was exposed to poultry infected with this virus. Next slide.

In the United States, and again, this is focused a bit more on what we know about the current situation among dairy cattle, as well as spillover into wild mammals and also poultry, these viruses thankfully have remained relatively genetically stable. When we look at the hemagglutinin gene of these viruses, and there's a phylogenetic tree on the right-hand side of the screen just depicting the evolutionary trajectory of this particular virus since it emerged in dairy cows, we are not seeing a lot of evolution of the virus, and we've seen only a handful of amino acid changes in the hemagglutinin protein. Most of those are sporadic changes that are not sustained from herd to herd. And so some good news is that these hemagglutinin changes do not appear to be impacting the antigenicity of the virus very much. I'll go into a bit more detail in a minute.

And then I think importantly, these are also mutations that do not impact the receptor binding domain, so we're not seeing changes that impact increased infectivity or that would be predicted to yield increased transmissibility among people. Having said all of this, there are a couple of changes that we have seen, both in dairy cattle and in some of the human cases that are found in antigenic sites, and I'll talk a little bit more about those and the results of our HI testing.

And then finally, one last point, looking across the full genome of these viruses, we have

not seen any mutations that are known to be associated with reduced susceptibility to FDA-approved antiviral drugs. Next slide.

So to focus back on the hemagglutinin protein and some of these amino acid differences that are detected. So as Dr. Kondor presented, we also focus on looking specifically at these amino acid changes that are occurring relative to the closest candidate vaccine viruses. So we use reference strains that are typically the candidate vaccine virus to give us an idea of how many amino acid changes are being detected in the hemagglutinin, and for the most part, again, this is a table looking across human cases of the 2.3.4.4b viruses in the U.S., as well as those that cause poultry outbreaks in Colorado and dairy cow outbreaks across the United States. We're still looking at only about two to four amino acid differences collectively compared to the closest candidate vaccine strain. And again, as I said, most of these are not found in antigenic sites, and those that have been detected in antigenic sites have been limited to really one or two viruses, what we would classify as sort of one-off, sporadic detections of amino acid differences relative to the common or consensus sequences of those viruses that are detected across a large number of animals. Next slide.

So this now is a hemagglutination inhibition assay looking specifically at ferret antisera developed to the 2.3.4.4b candidate vaccine viruses. So I'll focus your attention on the columns on the right-hand side of this table, beginning with RG71A, which is the Astrakhan CVV, RG78A, which is the American Wigeon, and RG80A, which is the chicken/Ghana CVV. And as you can see from looking at representative viruses, and this is specifically looking at cross-reactivity to a number of human cases that occurred in Colorado as well as one of the human cases that was detected in Michigan, we see that each of the ferret antisera arrays to these CVVs cross-reacts with these human viruses, with nearly equivalent heterologous HI titers,

indicating that there's good cross-reactivity of each of these three CVVs relative to viruses that have caused human disease. Next slide.

So this is also just to show some evidence that there are some reductions in a couple of viruses. This is a table that was provided by St. Jude Children's Research Hospital, another collaborating center here in the United States that also contributes to the VCM process. And through their testing, again, looking at viruses that had sporadic mutations in the hemagglutinin, specifically at antigenic sites that resulted in a gain of glycosylation, we see that there are some examples where the RG71A and the RG78A does have reduced cross-reactivity with these viruses, but that they are well covered by the chicken/Ghana RG80A, and this is because the chicken/Ghana strain also has that same gain of glycosylation around one of the primary receptor binding domains and loops that's a major epitope of these viruses.

So despite some indication that there is a couple of one-off strains that have reduced cross-reactivity, the vast majority of the viruses that have been characterized antigenically are well covered by each of the three CVVs that have been developed against the 2.3.4.4b viruses. Next slide.

So just to close, again, I wanted to put up this list of our available 2.3.4.4b candidate vaccine viruses. This is important because the final conclusion from the September 2024 vaccine consultation meeting was that we did not need to recommend a new 2.3.4.4b CVV based on the available data, most of which I've just shared with you through those genetic and antigenic slides. So we're holding steady in terms of our CVV production, working on completing the chicken/Ghana CVV, and -- next slide.

And then I'll just close with a brief summary, just showing that the epidemiology and the surveillance data, not only in the United States but globally, does continue to demonstrate that

the 2.3.4.4b H5N1 viruses are the predominant virus that's circulating in other regions of the world as well as in the U.S. There's been a number of infections in wild and captive mammals that have been reported. Of course, the ongoing outbreak in dairy cattle continues to be quite an issue, in my opinion, with ongoing spread among herds in California. Genetic analysis is showing that the virus is stable when we look at the HA, with very few amino acid changes that are sustained across herds and that are not being detected in other animal hosts, and that the antigenic analysis does show that the existing CVVs do cross-react with these viruses well, and there's currently no recommendation to develop new candidate vaccines to the 2.3.4.4b viruses. Next slide.

And that ends my presentation. Again, happy to take questions. Thanks.

CDC: Highly Pathogenic Avian Influenza A(H5Nx) Virus Surveillance and Characterization in the United States and Globally and Recommendations for Candidate Vaccine Virus Development – Q & A

Dr. El Sahly: Thank you, Dr. Davis, for the presentation and for all the work that went behind it. The first question comes from Dr. Offit.

Dr. Offit: Thanks, Todd, for that clear and thorough presentation. My question to you is, so H5 viruses to date bind to the alpha-2,3-sialic acid receptor, not to alpha-2,6, right? And until they evolve to bind to alpha-2,6, they're not going to be human pandemics yet. Is that fair to say? So you haven't detected any evidence that this virus has mutated or these viruses have mutated to bind to alpha-2,6. Is that true?

DR. DAVIS: That's correct, yes.

Dr. Offit: Thank you.

Dr. El Sahly: I also have quite a few questions, but I know we have a whole hour of discussion and you will be present, so I will save some of them for later. But did I read your tables

correctly that the Ghana subtype seems to be the most cross-reactive with the newer clades? I guess, did you call it the fifth clades? Or –

DR. DAVIS: Yeah, so not exactly. So the Astrakhan candidate vaccine virus does cross-react with the vast majority of the 2,3,4,4b viruses that have been detected. It's a small subset of viruses that are primarily circulating in West Africa that the chicken/Ghana CVV cross-reacts with better. And again, a small number, less than one percent of the total population of dairy cattle viruses, that have a mutation where the chicken/Ghana does provide better cross-reactivity.

Dr. El Sahly: Okay, so the Astrakhan. Okay, maybe we'll pull that slide in the hour that we have.

I see more questions. We're going to take the questions for the raised hands now, and in the interest of time, please save your questions. We will have a whole hour to discuss the topic. Dr. Chatterjee.

Dr. Chatterjee: Yes, thank you for your presentation, Dr. Davis. Could you go back a couple of slides?

DR. DAVIS: Kathleen, could you help to move back?

Dr. Chatterjee: I believe it's slide 26 that I had a question on.

Yes. So I was just looking at how long it takes for the candidate vaccine viruses to become available, and it looks like the one, the chicken/Ghana, it's been a couple of years, and we don't have those available yet?

DR. DAVIS: Yeah. So I think, you know, because chicken/Ghana initially was recommended to cross-react best with West African strains of viruses, there was a bit of a de-escalation in terms of the development of that CVV, because it became clear that the viruses covered by Astrakhan were the ones that really took off and were circulating across the globe and spreading into North

America.

Dr. Chatterjee: I see. Thank you.

Dr. El Sahly: Okay, thank you. Last question, Dr. Monto.

Dr. Monto: I see that some of your CVVs are N8. Why is that the case, since most of our strains right now are N1 that are of concern? It can't be safety because you've removed the polybasic cleavage site.

DR. DAVIS: That's right. Yeah, so, you know, again, during that period from about 2014 to 2020, there was a lot of re-assortment, and the viruses that were causing human infections –

Dr. Monto: So it's basically historic.

Dr. Davis: It's historic, and, you know, our assessment of ferret antisera and the antigenic characterization that it's done is really focused on the hemagglutinin gene. There are not many assays that characterize cross-reactivity with neuraminidase-specific antibodies, and so we don't actually infer much from the neuraminidase of these viruses anyway.

Dr. Monto: Except for the fact that our most used antiviral is neuraminidase-specific.

Dr Davis: Certainly for the antivirals, that is absolutely true, but not as much on the antigenic side.

Dr. Monto: Right.

Dr. El Sahly: Okay, thank you. I know the team will have a lot more to discuss, and we will have time shortly to do so. Thank you so much, Dr. Davis.

I'd like to invite Dr. Oshansky. Dr. Christine Oshansky is Director of Pandemic Vaccines and Adjuvant Program, Influenza and Emerging Infectious Diseases Divisions at BARDA. She will be discussing BARDA's Pandemic Influenza Preparedness and Response Program.

BARDA's Pandemic Influenza Preparedness and Response Program – Dr. Christine Oshansky

Dr. Oshansky: Great. Thank you so much. Good morning, everyone. Thank you for the opportunity to allow me to discuss a little bit about vaccines for pandemic influenza preparedness and response here in the U.S. So next slide, please.

Okay. So a little bit about our pandemic preparedness policy in the U.S. So the U.S. government has established several pandemic preparedness goals under various plans that I've listed here as snapshots, and each of these plans can be found on CDC's Pandemic Influenza website, so those links can be accessed there. But when you look through these plans, the goals include delivery of first-finished doses of pandemic vaccine within three months of a pandemic declaration, having sufficient supply to meet public demand within four months of a declaration, and the manufacture, fill, finish, release, and delivery of enough vaccine for the entire U.S. population within six months of a declaration.

So in order to meet these goals and to, frankly, enable rapid response, BARDA continuously maintains influenza virus vaccine seed lots and some quantities of antigen and adjuvant. We manufacture clinical trial vaccine lots and conduct clinical trials to understand the immune response in terms of safety and immunogenicity so that we have data on hand when we need it. Next slide, please.

So in our -- our program is formally titled Vaccine Medical Countermeasures for Pandemic Influenza and Emerging Diseases -- Diseases Preparedness and Response Program, and as part of this program, we manage the U.S. National Pre-Pandemic Influenza Vaccine Stockpile, or the NPIVS, and this is very different from the Strategic National Stockpile that is also managed by the Administration for Strategic Preparedness and Response, or ASPR, so we are quite different. But this program was formally initiated in 2005, and really importantly, it

leverages the existing infrastructure and capability here in the U.S. to support preparedness and response.

So we at BARDA have maintained contracts with the FDA-licensed influenza vaccine manufacturers, and this allows fast and continuous updates, like I mentioned just a few minutes ago, fast and continuous updates of pre-pandemic influenza virus vaccine seed lots. We can produce influenza virus for the conduct of clinical trials, and as funding allows, we can manufacture bulk drug substance and/or final container antigen and adjuvants that we can stockpile for pandemic readiness purposes.

Now, anything that is manufactured gets placed into storage and entered into stability monitoring programs. These are all within the respective manufacturer's quality systems. Now, because we have contracts in place, it also allows quick response in the event of a pandemic, because everything is already in place and ready to go in terms of negotiation.

So the NPIVS, or the U.S. National Pre-Pandemic Influenza Vaccine Stockpile, is currently composed of adjuvants, AS03 and MF59, and that's because these two adjuvants are part of licensed influenza vaccines already, as well as pre-pandemic influenza virus bulk antigen, so this is drug substance, as well as final containers of vaccine that's manufactured from candidate vaccine viruses representing virus subtypes regarded to have the greatest potential to cause a pandemic. So, our current program includes really strong partnerships with CSL Seqirus, with GSK, and with Sanofi.

So CSL Seqirus can manufacture cell-based antigen, as well as MF59 adjuvant domestically here in the U.S. GSK can manufacture AS03 adjuvant domestically here in the U.S., and Sanofi can manufacture egg-based and recombinant protein-based antigen here in the U.S. So like I said before, we're really utilizing facilities that can currently produce domestic

and licensed seasonal influenza vaccine for immediate response capability at commercial scale. Next slide, please.

So as we consider what a large-scale response might look like in the U.S., our current pandemic influenza vaccine response plan is made up of three components. The first two will make up the bulk of the response in terms of numbers of doses that would be able to be manufactured in an emergency. So the first large component in terms of numbers of doses is CSL Seqirus' cell-based influenza vaccine that's co-formulated with MF59 adjuvant. So this is manufactured using the AUDENZ process, and AUDENZ is approved for use in individuals six months of age and older.

The second large component in terms of numbers of doses in the large-scale response is Sanofi's egg-based influenza vaccine mixed at the bedside with GSK's AS03 adjuvant. Now as you know, this is not a licensed product, but because we must leverage existing domestic capability here in the U.S., and we know that Sanofi is the largest supplier of influenza virus vaccine antigen in the U.S. This is included as a major component of our vaccine response plan in an emergency. Sanofi's H5 vaccine is licensed as antigen only and is indicated for use in individuals ages 18 to 64.

Now, the third component of our vaccine response plan, which is no less important but simply more modest in terms of numbers of doses that might be available for the U.S., is GSK's egg-based influenza vaccine, which is mixed at the bedside with AS03 adjuvant. The reason for this is because GSK's antigen is manufactured outside the U.S. with pandemic commitments to other markets. However, the U.S. has procured some antigen final containers and bulk antigen for pandemic readiness purposes, and you know that GSK's H5N1 adjuvanted vaccine is approved in the U.S. for use in individuals six months of age and older.

Now, I'd be remiss if I didn't mention mRNA-based vaccines. MRNA-based vaccines are not part of the current preparedness activities in the U.S. However, BARDA is planning for potential future responses. As you know, nucleic acid-based seasonal influenza vaccines are not yet licensed here in the U.S., but if they were to become licensed here in the U.S., then pandemic influenza response plans would be reassessed, and then those would be incorporated into our vaccine response plan as appropriate. Next slide, please.

So how do we make decisions about pre-pandemic influenza virus vaccines? Here in the U.S., we have an interagency decision-making body, which serves as a venue to discuss issues related to U.S. government response to influenza in general. So there are subgroups that focus on zoonotic influenza, seasonal influenza, other topics like diagnostics and treatment, and through this forum, subject matter experts from across the U.S. government will review influenza preparedness and response efforts. And so this includes relevant influenza epidemiologic and zoonotic surveillance data that is happening -- that is being generated across the world.

So based on this information, decisions are made using a metered response approach, and so one example of this is CDC's Influenza Risk Assessment Tool, or the IRAT. And so where any particular strain might be assessed for its risk of emergence as compared to its risk -- its impact on public health. And as these risk assessments are incorporated into the decisions, the decisions are implemented, and some of these implementations may include having virus vaccine seed lots being manufactured at each of the manufacturers, or perhaps we go ahead and manufacture bulk lots, so that's the equivalent of a bulk drug substance, or maybe we conduct a clinical trial. Now, in the event of an emergency -- a public health emergency, we would initiate large-scale manufacturing as funding allows. Next slide, please.

So BARDA is always in a state of preparedness, and this is a more simplified timeline

from what Todd -- what Dr. Davis was showing, but since we're always in the state of preparedness, we immediately began preparing for Influenza H5 Clade 2.3.4.4b after the 2.3.4.4bs began to be found in wild birds and then in commercial poultry in early 2022. We immediately contracted the influenza vaccine manufacturers to prepare master and working virus vaccine lots -- vaccine seeds for manufacturing readiness. And then in April, the first H5N1 human case was reported in Colorado, and we not only had initial vaccine manufacturing begin, but we contracted for the conduct of two clinical trials to test the A/Astrakhan H5 vaccine. One trial is sponsored by CSL Seqirus, and the second is sponsored by GSK, and I'll come back to those in just a minute.

As influenza H5 2.3.4.4b continued to be found in birds and mammals throughout the Americas, BARDA began preparing for a third clinical trial to test Sanofi's egg-based A-Astrakhan H5 vaccine, and most recently, since about April 2024, using additional funds allocated to BARDA, we executed additional contracting actions that will result in more finished vaccine doses, additional bulk drug substance, and physical and chemical compatibility studies to ensure that data exists to support administration if needed. Next slide, please.

So the next three slides I'm going to talk about the three clinical trials that are underway. The first clinical trial is sponsored by GSK. It's a phase I/II randomized clinical trial to evaluate the safety and immunogenicity of different formulations of monovalent A/Astrakhan H5N8-like virus vaccine with ASO3 adjuvant system. So this is given as a two-dose series to adults 18 to 64 years of age, and those adults ages 65 and above. Like I said, it's a two-dose series given 21 days apart. The status of this clinical trial is that enrollment is complete and final analyses are underway. The outcomes include safety and immunogenicity.

So safety, we're looking at the safety and reactogenicity of the different formulations

adjuvanted with ASO3, and then for immunogenicity, of course, we're looking at hemagglutination inhibition antibody responses and microneutralization antibody responses against the A/Astrakhan H5N8-like virus, and the primary endpoint for this study is at day 43. So that's 21 days post-dose number two. Next slide, please.

So the second study I wanted to talk to you about is sponsored by CSL Seqirus. This is a phase 2 randomized clinical trial evaluating the safety and immunogenicity of homologous or heterologous priming and booster vaccinations with the A/Astrakhan H5N8-like virus vaccine or the A/Guangdong H5N6-like vaccine adjuvanted with MF59, and these are manufactured in cell culture. So again, we're looking at two doses, 21 days apart as the primary endpoint at day 43, and then each of these groups receives a third dose six months later. The status of this clinical trial is that enrollment is complete, and like the other one, final analyses are underway. And the next slide, please.

This is actually my final slide. So this third clinical trial is sponsored by BARDA, and this is what we refer to as a mix-and-match trial. So because the Sanofi egg-based antigen mixed with adjuvant is not licensed here in the United States, BARDA sponsors these clinical trials to make sure that the data exists if it were to be needed for emergency -- to support emergency use authorization as appropriate. So the title of this clinical trial is it's a randomized phase 2 study to assess the safety and immunogenicity of H5 monovalent influenza vaccines at different dose levels adjuvanted with either ASO3 from GSK or MF59 from Seqirus. And, again, we're generating the data if we need it in the event of an emergency.

So the status of this clinical trial is that we're still recruiting. We just had first subject, first visit back in August, so we're getting close to full enrollment, and the study will be underway. The outcomes of this study include safety and immunogenicity, just like the others.

So we're looking at the safety and reactogenicity following each vaccination of the antigen and dose of vaccine given with ASO3 or MF59. And immunogenicity, like the others, we're looking at hemagglutination inhibition antibody responses and microneutralization antibody responses against the A/Astrakhan H5N8-like virus, as well as the influenza A/bar-headed goose/Qinghai H5N1-like virus at various time points post vaccine. So these are given as two doses, 21 days apart, with a primary endpoint at day 43. And I've listed the clinicaltrials.gov numbers at the bottom of each of these slides so you can have access to those files as well.

So I think that's actually my last slide. Thank you very much for allowing me to participate today, and happy to take questions.

BARDA's Pandemic Influenza Preparedness and Response Program – Q & A

Dr. El Sahly: Thank you so much, Dr. Oshansky, for this. I guess one question pertains to the antigenic relatedness between the Astrakhan, which seems to be the predominant strain that's being evaluated, versus the bovine strain or strain-like that's currently circulating. I know there's relatedness, but do we have metrics around that?

Dr. Oshansky: So like Dr. Davis was mentioning, the A/Astrakhan based on ferret -- based on serum raised against the A/Astrakhan, it does have good cross-reactivity to the bovine viruses. So we expect there to be protection if this vaccine were to be used.

Dr. El Sahly: Okay, thank you. I wonder if, Dr. Davis, you can prepare those data for sharing during the one hour we have for discussion.

And I do see a lot of raised hands, so I will remind everyone that please be brief, and we will have a whole hour to discuss with Dr. Oshansky and Dr. Davis. Beginning with Dr. Perlman.

Dr. Perlman: Yes. So thank you for that great talk. One question. So one of the things that BARDA does is think ahead. So if it turns out that the H5N1 or H5N6 or whatever virus doesn't

really match the ones that we have, and it also exhibits a human-to-human spread, what are the -- what is BARDA thinking about what it will do in that circumstance? Because a lot of these vaccines will take quite a while if we have to start from scratch. And you mentioned mRNA vaccines, but they're not licensed. Do they work for HA and potentially neuraminidase? How are you thinking about that?

Dr. Oshansky: Well, so mRNA-based vaccines, like I mentioned, aren't part of our current response plans. That doesn't mean that in an emergency we wouldn't work with those manufacturers. However, for -- we -- so in terms of surveillance, you know, we work with CDC and other WHO collaborating centers, and we are monitoring the surveillance very closely of zoonotic strains, you know, the animal viruses that are circulating around the world. And so we constantly update what is represented in the U.S. National Pre-Pandemic Influenza Vaccine Stockpile. And so the A/Astrakhan H5N8 is just one that's represented. And back in 2022, when all of this was beginning, we went ahead and that's why we were so proactive in getting these clinical trials underway. We have manufacturing underway. Right now we have additional manufacturing underway that -- so just in case there's an emergency, we can access those doses.

Now, if a new strain were to emerge, we would do the same steps, but we would accelerate it as much as possible.

Dr. Perlman: Okay. Thank you.

Dr. El Sahly: Now, there's always the notion that a less effective vaccine in a pandemic is better than no vaccine while you're waiting on the full-on matching vaccine, but it's all speculative. Dr. Rubin?

Dr. Rubin: Thanks. I wanted to follow up on Dr. El Sahly's question from before. It seems like in the clinical trials that you're doing right now, that adding in antigens from the current catalog

break wouldn't make sense, particularly the -- as we saw earlier, there are some escape mutants that have poor cross-reactivity with the ferret serum raised against the Astrakhan strain. So I wonder if that -- you're thinking about that at least as a post-hoc analysis for the ongoing clinical trials.

Dr. Oshansky: Yes, we are. So at the time of these clinical trials, the bovine viruses did not exist, so that was pre-cattle, you know, outbreak. What we will be doing is as these clinical trials come to a close in the spring of next year, we will plan to take that serum and assess the cross-reactivity of the vaccine serum with the currently circulating viruses.

Dr. Rubin: Thank you.

Dr. El Sahly: Or the serum from those who were infected in Colorado and elsewhere against the -- I guess the strains that are in clinical testing. So sort of the reverse, but –

Dr. Monto.

Dr. Monto: I was wondering about a couple of things. One, in your clinical trials, are you evaluating the use of an unadjuvanted booster the second time? Because as I recall, in the studies that were done in the 2000s, there was almost as good response there. As Dr. El Sahly pointed out, any vaccine more widely distributed is probably better than no vaccine.

And the other question I have is, Seqirus has only a cell culture component. That's not going to produce very much vaccine. If we have a pandemic, are there thoughts about supplementing in terms of sources?

Dr. Oshansky: Yeah, so I'll take your second question first. So, yes, CSL Seqirus can manufacture cell-based influenza vaccine here in the United States. They are a major component of our response plan. In addition to CSL Seqirus's cell-based vaccine, Sanofi's egg-based vaccine that would be mixed with GSK's ASO3 adjuvant would be the second large component

of our response. Now, your first question, I apologize, can you restate it?

Dr. Monto: I asked about trying different strategies in terms of the boosting with non-adjuvanted.

Dr. Oshansky: Yes. So that is a good question. It is not part of our current clinical trial designs at either of the two manufacturers at CSL Seqirus or GSK or the BARDA-sponsored study. And the reason is because we consider -- we have to consider the distribution rollout, and so what it would look like in the field. And so, if you're mixing and matching different versions, some are getting antigen-only, some are getting adjuvanted vaccine, it is a little bit more complicated. So we're trying to simplify that in terms of our clinical trial design.

Dr. Monto: Are there –

Dr. Oshansky: It doesn't mean that it can't be done, it just is not –

Dr. Monto: Where are you going to have shortages with antigen sparing? Is it going to be in the antigen or in the adjuvant or both? That's the question.

Dr. Oshansky: We are typically adjuvant-constrained, you're right, but we have a large stockpile of ASO3 that was manufactured for the COVID-19 response, so we would rely on that. And we have access to MF59, of course.

Dr. Monto: Thank you.

Dr. El Sahly: Last question from Dr. Gans.

Dr. Gans: Hi. I realize we'll have a discussion later, so just a really quick question. Are you looking at the immunogenicity after one dose versus the two doses? Just thinking about if we're, like, in a pandemic situation and, you know, having immune responses more quickly than not would be relevant?

Dr. Oshansky: Yes, absolutely. So our time points include time -- you know, day one prior to

vaccination, as well as day 22, so that's three weeks post-dose one. Then they get the vaccine, and then – the primary endpoint, though, is day 43, but the other time points are still included, even a six-month follow-up till we get that long-term immune response data point.

Dr. Gans: And so, forgive me, when will those data be available?

Dr. Oshansky: We expect all three clinical trials, actually, will have interim data from the BARDA-sponsored study in spring of next year, and then the final study data would be available from the two manufacturers in the first half of next year.

Dr. El Sahly: Thank you. Thank you, Dr. Oshansky, for the presentation.

So on the agenda now, we have the lunch break. The lunch break will be 30 minutes, after which we will have a whole hour to discuss the pandemic flu question with Dr. Oshansky, Dr. Davis, and FDA leadership. So we will reconvene at, let's say, 12:20. Is that good? Eastern.

Committee Discussion – Topic II

Dr. El Sahly: Okay, welcome back everyone. This will be the time where we will be having the discussion for Topic two. Topic two is the pandemic, the change in the strain for the pandemic vaccines. We heard two presentations one by Dr. Davis, one by Dr. Christine Oshansky. Very informative and I'm pretty sure a lot of you have questions. We only had a few minutes, but now is the time to ask those questions.

To set the stage for the discussion, please look at the screen to see the discussion topics which is input on the proposed strain change process during the inter-pandemic period and whether a change to the current composition of licensed prototype vaccines using the proposed process is needed for preparedness purposes and whether the candidate vaccine viruses are available that are appropriate to update currently licensed prototype vaccines. Many hands are up, and we will begin in the order they appear on my screen, which would be Dr. Offit. Dr. Offit?

Dr. Offit: Yeah, thanks, Hana. I'm trying to understand one thing. There is a vaccine, an H5N8 vaccine that is currently used in Europe and it's a recommended vaccine for those who work in high-risk industries like dairy, poultry, fur. So I -- can one assume then that that vaccine, that the H5 component of that vaccine is matching the H5 strains that are circulating in Europe, which brings me to my next question.

We have, obviously, dairy workers who are at risk here too, but we don't have a recommendation, at least to my knowledge, by the CDC for people who work in high-risk industries here. Is that because these bovine strains are too distinct from, say, the Auden's vaccine that we have that was licensed in 2020, so that it wouldn't be worthwhile? Is that a fair assessment?

Dr. Davis: I think I could at least start with the first question related to the AstraCan H5N8 vaccine that's being used in Europe. So, yes, so the data that is analyzed during this vaccine strain selection meeting, and including the most recent meeting we had just a few weeks ago in September, does show that the AstraCan CVV and ferret antiserum rays to that CVV is broadly cross-reactive against, you know, what we would consider to be antigenically related H5N1 viruses that are circulating among European poultry and wild birds as well.

Dr. Offit: And then in terms of here, in terms of the U.S., we also have dairy industry workers or poultry industry workers who are at risk, but we don't have a recommended vaccine. Can I assume that's because the bovine strain that has since come up since that 2000, say, 2020 licensure of the vaccine is too distinct from the current H5 circulating strains?

Dr. Davis: No. In fact, the data is showing that the AstraCan CVV is also broadly cross-reactive against bovine viruses and other H5s that have been detected in poultry. But, yeah, I see Jerry's hand up. Maybe, Jerry, I'll defer to you to address the question about vaccine utility.

Dr. Offit: Yeah, why we don't have a recommendation here if those strains are close?

Dr. Weir: So, Dr. Offit, I don't, as Dr. Davis said, it's not how closely the strains match. I think what you're referring to and talking about is essentially vaccination policy question, not a composition question. In Europe, the choice to vaccinate in at least one country was driven by unique circumstances because they have a lot of fur farming. Here, vaccination policy questions would be sort of addressed by an interagency group as well as ACIP, and that's not really what we're talking about. But I think you can assume that it's not because it doesn't match. As Dr. Davis shows, the match is actually pretty good if we decided from a vaccination policy point of view that we should do it for anyone.

Dr. Offit: So, Jerry, do we not think that the disease is as big of a threat here to allow us to make that recommendation? Is that it? I know this isn't you, this should be the CDC, but is that your sense of it?

Dr. Weir: Yeah, you're sort of asking an opinion question, but I think that the fact that we haven't made any sort of recommendation does say that, yes. But again, this would be outside the purview of this committee and it would be a more global, not global, it would be more of a U.S. government decision as well as CDC, ACIP, all of that for vaccination policy of what to recommend and for whom.

Dr. Offit: Thank you.

Dr. El Sahly: Thank you. Dr. Offit, Dr. Berger?

Dr. Berger: So, here's a question for Dr. Davis, and I was going to ask it earlier, but, you know, I've been sitting here thinking about process, and you mentioned early on that the goal is really to identify virus antigens that were going to elicit immunity against the breadth of viruses that co-circulate in the future, that they provide immunity across multiple subclades, and that you're not really trying to match against a specific strain that's circulating, but taking into account different factors, such as what are the genetic subclades that are in circulation, where they're actually circulating, what geographic or what genetic differences are coming up, and other factors. I guess what I'm thinking about is sort of the long term. We've been asked to think about the composition and how we would be coming together as Birkbeck to make a recommendation in the future. What I'm wondering is how would you weight each of those different factors that you put out there as essentially criteria for identifying zoonotic candidate vaccine virus development, so that we have a better sense when, if the process that's actually being laid out for us in the future is us coming together, so that we can take these into account in a proper way. And I'm thinking about things like geographic diversity. Is this something that should be weighted higher than something else? Cross-reactivity obviously is a huge one. I'm just trying to get a sense of how you view these different factors.

Dr. Davis: Thanks. Maybe it's obvious. I think the first of which is these molecular changes that really would change the receptor binding specificity in these viruses. That's something that we always look at initially, is to be sure that these viruses are still binding to avian receptors. I think that would change our trajectory and decision making quickly if we were to see a virus that had mutated in the receptor binding domain to indicate increased opportunity for human cellular receptor binding and leading to infectivity and transmissibility. That's probably the first thing that I would focus on.

Other than that, yes, the 2344Bs are a good example where geographic distribution is huge. When you see a virus that clearly has spread around the globe in a very short period of time, then we can focus our efforts not just on, let's say, US-centric decision making, but something that would be applicable across the globe. I think that's important to consider as well.

Then finally, in this inter-pandemic period, we will continue to recommend and develop these pre-pandemic kind of vaccine viruses that do provide that broad cross-reactivity against a number of different clades. I think then the question is at what point do we consider one of those an optimal vaccine that does offer that breadth that we're looking for? That's exactly the strategy that we use in our testing. We want to be sure that we've got the reagents and even the developed CPVs against this very long list now of pre-pandemic candidate vaccine strains that really represents the optimal antigen. Then that's where our collaborations with BARDA come in handy because we want to know in a clinical trial setting, are they performing well? Is there immunogenicity that would encourage us to then select one of those broadly cross-reactive CPVs that could be applicable across the globe?

Dr. Berger: Thank you.

Dr. El Sahly: Dr. Gans.

Dr. Gans: Thank you so much. I had a similar question to Dr. Bergman where I was going to ask about the attention, as you said, Dr. Davis, just to the way in which the virus is changing to become more transmissible or more adapted towards human slash/mammalian before an outbreak happens. I guess one of my questions around that now, since you answered the first part of that, do we feel like these sort of -- how in the interval from these six-month time points when you all come together to look at some of the data, is there sharing of that so that we actually don't

have to wait, for instance, for outbreaks in our cattle outbreaks, things that we're sort of seeing clinically, or maybe that is what prompts the testing of these, I don't know. I'm just wondering, is there a better way to predict how these viruses go in terms of their transmissibility so we could actually be more prepared in that way?

My other question to that happens in regard to how I think these surveillance systems are amazing, and I really appreciate them in terms of how we would hopefully become prepared for something that is a little bit hard to predict from the data that you propose in terms of the geographic specificity and anyway. But I know that at least there was some suggestion that other types of vaccines are being looked at in terms of messenger RNA and things that make us a little bit more quickly adaptable to some of the changes that we're seeing. Is there more work happening in that in this instead of just going for the usual ways in which we make these vaccines so that potentially we could be more prepared more quickly?

And then my final question, but it sounds like this is happening, I'm assuming that as these VCCs are being produced, and hopefully the studies that are happening with any studies, there is a large bank of serum that we can continue to test on new emerging strains. Thanks.

Dr. Davis: Yeah, thank you, Dr. Gans. So to start, so even though we summarize all of this for publication on a six-month basis and do really think hard about the recommendations at that cadence, there are ongoing teleconferences that we have among members, both collaborating centers, as well as the H5 reference labs and those of flu veterinary laboratories. We're constantly sharing reagents that are generated because we need the reagents to be able to do the testing for the next six-month period. And then when there are specific events, so like the dairy cow outbreak in the United States, we will convene special sessions of those participants within the VCM to have exactly that conversation. What data do we have? What data do we need? And the

WHO, even back in May of this year, published a report that was based primarily on CDC and St. Jude Children's Research Hospital data, looking at the genetic and antigenic data that we had compiled for the dairy cow viruses. And that is an ongoing process. So we do have some intervals where we can communicate and recommend new CVVs outside of that six-month reporting period if we need to.

The other question around other vaccine platforms, yes, there's quite a lot of work being done, of course, on the messenger RNA vaccine. In the NIH and the SEER network that I mentioned, there are some active investigations that are being funded to explore even H5 messenger RNA vaccines and their utility. Again, those are focused primarily on in vivo animal models to date. We have some research collaborations with messenger RNA vaccine manufacturers, where we are also doing the same at CDC, so that we can assess the breadth of coverage against things like the dairy cow viruses. And then finally, I think the other part of this is the coordination with BARDA. And Christine, I see your hand raised, so maybe I'll pass it over to you just to expand on this.

But through the collaborations with BARDA, the ultimate goal is that when clinical trials are completed and the manufacturers are able to get their data out, that that sera that is produced gives us another reagent that we can use to constantly assess the antigenic landscape of these circulating viruses relative to clinical trial sera that's produced in humans. But Christine, anything else to add there?

Dr. Oshansky: Yeah, thanks, Dr. Davis. No, nothing to add on the serology piece. You're exactly right. I did want to add some more comments on the mRNA-based vaccines. So while they're not -- I mentioned during my piece, they're not part of our current preparedness activities. But that doesn't mean that we're not planning for future responses using mRNA-based vaccines. So we

are really leveraging the existing infrastructure and capability like I mentioned here in the domestic U.S. But we have entered, BARDA has entered into a partnership with Moderna recently to support advanced development of an mRNA-based pandemic influenza vaccine, specifically H5. And that contract includes, if needed, procurement. So, you know, this is underway. So phase three clinical trials are expected to start next year in 2025. So we're getting closer to having a pandemic influenza vaccine, an mRNA-based vaccine licensed.

Dr. El Sahly: Did you say phase three?

Dr. Oshansky: That's right.

Dr. El Sahly: Against H5? That would be maybe... I think it's looking at immunogenicity would be the end point.

Dr. Oshansky: That's right.

Dr. El Sahly: Okay. All right. Thank you. Okay. Dr. Chatterjee?

Dr. Chatterjee: Yes, my question is for Dr. Oshansky. I realize that the clinical trials that are being run right now with these candidate vaccines are in pretty early stages.

But I'm wondering if there are plans to study them in special populations: children, immunocompromised hosts, people of different racial and ethnic backgrounds?

Dr. Oshansky: Yes, thank you for the question. We do have enrollment targets for diverse populations. So we're trying to include that into these clinical trials. As far as pediatrics and special populations, those require additional considerations, additional funding because Auden's and GSK's H5N1 vaccine are already licensed down to six months of age in terms of pediatrics.

We haven't been including that piece of it, but it is on our list. But, again, it is all contingent upon funding.

Dr. Chatterjee: Thank you.

Dr. El Sahly: Dr. Rubin?

Dr. Rubin: Hi, thank you. I have a question about, the human disease that's been seen in the current H5 cattle outbreak. A lot of the disease has been mild, as you noted. Is there decent serosurveillance? Because they're, presumably, if there's a lot of mild disease, there must be a lot of asymptomatic infection.

Dr. Davis: Very good question. Yeah, so as you noted, yes, the clinical symptomology has been relatively mild, with conjunctivitis as the primary symptom of those that have been exposed to H5 in the U.S. Part of that is most likely the route of exposure, especially among individuals that have very close contact with animals and their secretions, that's likely leading to the symptoms that we're seeing. PPE usage is, is a part of that, despite obvious complications with being sure that appropriate PPE is used in all situations. We do think that PPE is helping to reduce that route of exposure in individuals. When they are detected, they're being offered oseltamivir quickly. And so we think that that might also be reducing the clinical severity of illness as well.

And then finally, you know, I think, just sort of get to your question on serology. This leads to this assumption that there might be more human exposure even if mild illness in -- this at-risk population that has contact with infected animals. And the CDC is currently working with several states to be able to conduct those serology studies. So we're currently conducting seroprevalence studies in farm workers in both Michigan and Colorado. Those data are still

pending. And so there's analysis being done as we speak. And then there's also been some efforts to look at seropositivity among veterinarians that have also had close contact with infected animals. And so just a few weeks ago at a conference for the American Association of Bovine

Practitioners, there was serology study that was conducted among veterinarians, and other farm workers that have had contact with animals. And so a lot of that data is not out yet. so more to come, but that's something that we want to be sure we understand, so that we really get a handle on just how many may have been infected that otherwise didn't present with severe enough disease to even get tested. Over.

Dr. El Sahly: Thank you, Dr. Rubin. I have a follow-up question to this, somewhat related. So with the older clades, the Vietnam and Indonesia, the, the 2.2.2, there was a mortality of 30%. It was a very severe influenza in healthy young persons or anyone of all ages is how I remember it. And then when H5N8 started, which I think began, I guess the clinical cases, the earliest clinical cases were in Russia. Things became more on the subclinical, minimally clinical spectrum. And we stopped hearing these very high morbidity, mortality numbers with the disappearance of the older clades. Is my understanding correct, or are there data that will be coming, that will give us a better understanding?

Dr. Davis: No, that's right. And so, you know, historically, if we look at the numbers, we're just looking at the numbers, the case fatality ratio with H5N1 has been very high, even higher than 30%, close to closer to 50%, collectively. There has been a lot of genetic variation in these viruses. Some viruses do have mutations that we know will result in a more severe infection in an animal model, for example. And we think that probably does translate to some severity of illness in humans. those thankfully are not circulating anymore so that the genetic features certainly have some impact. But the H5N8 that emerged to cause poultry outbreaks and wild bird

infections around the world I think it also enhanced our diagnostic testing. I think a lot of people were paying more attention to those that were exposed to infected flocks. There were several individuals in multiple countries in Europe, where they tested positive, but they had very mild illness. There's even some speculation as to whether they were even infected with the virus rather than just being contaminated in their nasal turbinates when they were sampled, because they were exposed to higher environmental contamination of viruses.

One of the cases in the U.S. in 2022 in Colorado, I personally believe it was not a true infection, but the person just happened to be sampled on the same day that they were involved in culling operations. So there is this mounting evidence, that whether it's mild illness, because of some changes in the virus or the rot of exposure, or, whether or not these folks are being tested at just the right time to pick up viral RNA, those are some of the questions that we don't completely understand, but there is mounting evidence, that things have perhaps shifted in our behavior towards these viruses, the testing strategies, and the reporting of cases.

Dr. El Sahly: I mean, I would think if we are, at least since the Russian or the outbreak in 2020, if our diagnostics and proactiveness at pursuing diagnostics has increased, we should have probably picked up even more, but we're not in terms of meaningful severe disease, pneumonia, death, which is 30 to 50% with the older clades. But anyway, well, that's a reassuring development. Dr. Monto.

Dr. Monto: But isn't it true that there are the same clades causing severe disease and in Southeast Asia and Cambodia, places like that.

Dr. Davis: Yeah, that's absolutely right. And so again, I think for the sake of this conversation, a lot of it is focused on the two, three, four bees. There are other clades, as I

mentioned, still circulating in the Mekong Delta region, which still continue to have severe illness, pneumonia, and even fatal infections. So, there is some specificity, to the two, three, four, four bees that makes them a bit different from what we've previously seen.

Dr. Monto: It may be the clades in other words.

Dr. Davis: Clades. I also have to believe it's where these viruses are detected and who's exposed to these viruses. Are they getting treated quickly? Do they have the ability to be tested within days of symptom onset and things like that, that I think also predict the outcome.

Dr. Monto: Right. What I really was, raising my hand to discuss is looking at the discussion topics. I think from our experience in 2009, the proposed strains, change process will work with the modifications that Dr. Weir talked about. in other words, there's got to be some testing with strain selection there really isn't much of any testing, but it can't be too much. I remember in the 2009 period, some of us had to remind people who wanted to have a lot of testing that pandemic outbreaks don't wait for the winter season and you better have your vaccines ready, which was really the case. Things moved pretty quickly in 2009 and we weren't caught in the U.S. in the trap of producing, adjuvanted pandemic vaccines, which much of the rest of the world got into largely for regulatory reasons and the fact that they didn't have, appropriate testing of just using, the strain selection process.

I think it's harder to talk about the second discussion topic and one of my concerns, we've heard this, with the mRNA vaccine discussions is whether we have to make sure that the platform doesn't drive the process. In other words, a platform of similarity, in production to seasonal vaccines, so that, innovative vaccines, even though they are not, previously licensed can be considered, and also that we move a little quicker because the one lethal case of H5N1 might

change the process in terms of the alarm bells, sounding. We haven't had a severe case, but the whole story of the unpredictability, the lack of ability to protect dairy cattle spread, is a lesson to be prepared for the unexpected. Thank you.

Dr. El Sahly: Thank you, Dr. Monto. And I have a clarifying question pertaining to the circulation of the older clades. So, I understood that they, for the most part, are no longer circulating, but Dr. Davis, you pointed out that they are in just in more restricted geographic regions. Is that correct?

Dr. Davis: That's right. Well, yes and no. And there have been many, many clades that we now believe are extinct. And so over time there have been clades that have just disappeared. They've likely just been replaced, by more variety.

But it is true that at least in the Mekong Delta region of Southeast Asia, the 2321C viruses, which are genetically and antigenically different, 2344B, those remain in circulation. They're maintained in a lot of the duck populations, that are resistant to vaccination that's been attempted across the region in birds. So those are still out there.

And then in India, Nepal, Bangladesh, there are still 2321A clades that circulate in poultry populations in those countries as well. So there are still some lingering clades that represent these more historical viruses.

Dr. El Sahly: Okay. And when they spill over, they cause the, at least as far as we know, with the limited epidata, they cause a disease that is more similar to the Vietnam, Indonesia type clades, right?

Dr. Davis: That's correct. Yes.

Dr. El Sahly: All right. Thank you so much, Dr. Davis. I see a question from Dr. Portnoy.

Dr. Portnoy: Great. Thank you. I guess Dr. Manto, I wanted to, kind of go on Dr. Manto's point, because what his point was is similar to what I wanted to say. In 2009, H1N1, emerged in the spring. And by summer, the hospital I worked out was filled up with patients who were sick with the influenza. It was a big problem. Patients were begging for the flu vaccine. They want to know when is the vaccine coming? Can I get the vaccine? They were constantly asking for it. And there was no vaccine.

By the time the vaccine became available in October, the, the, the anxiety about it had decreased and the patients were no longer not only asking about it, but that anti-vaccine misinformation had entered into the population. So when I started offering the vaccine to my patients, a lot of them turned it down. They heard that it was a bad vaccine, that it was, couldn't trust it and all of that stuff.

My point is the rapidity of the response is absolutely critical. If we don't respond in a timely manner, a lot of people get sick very quickly and then people refuse to get the vaccine because of misinformation. We have to be able to provide vaccines quickly. we have different technologies, but my understanding is that the one technology that is likely to be the most rapid response, the mRNA, is the one that's not being emphasized. And I want to know why is that the case? Why are we not putting most of our efforts into promoting the technology or the platform that can give us the most rapid vaccine? Because it's important that the vaccine be effective, absolutely. But if it's too slow, it's not going to work because people just won't take it. Thank you.

Dr. Oshansky: So I think I can, start by answering and others can fill in. So the reason we are not including that as a major component of our, vaccine response plan is because it is, as you know, not yet licensed in the U.S. So that infrastructure for influenza, vaccine manufacturing is not quite there yet. So it doesn't mean it won't be, it just isn't there today. And so that's why -- so BARDA, I just mentioned, you know, we've entered into a partnership with, Moderna. We have solicitations out on the street looking for other partners for this. And so we're, we're working towards that.

Dr. Portnoy: Yeah, but six months is too long. People are just not going to take the vaccine if it takes that long.

Dr. El Sahly: Oh, I see Dr. Weir, maybe you have a comment, Dr. Weir?

Dr. Weir: Yeah, a couple. first of all, a couple of comments, they're quick. first of all, the 2009 example, in that example, we did not have a CVV at the time that virus emerged. And that is what, as Dr. Davis has tried to point out, we have made, again, things are unpredictable, but we have made enormous progress in expanding the sheer library of CVVs. And while, again, it's unpredictable, we are definitely in better shape than we were in 2009.

The other part of that that we didn't talk about here is of course, developing these vaccines also requires other things like reagents. And in 2009, since we didn't have a CVV, we certainly didn't have reagents either. That takes time as well as just the regular manufacturing concerns. So we started from scratch then. Now we have a much better library of CVVs. We have a lot of effort ongoing in different parts of the world to develop reagents and certainly pilot lots of reagents so that we're better prepared there.

Back to the MRNA, while BARDA has told you their philosophy and why they're focusing on certain things, that doesn't mean that that's the only efforts going on. Without revealing anything proprietary, I can tell you that there is plenty of action in the MRNA vaccine development world from all sorts of sources and we see it all the time. So a lot of work is going on to develop these vaccines and find for MRNA vaccines and even other platforms and find out if they will work. And that is important in the inter-pandemic period, but a lot of work is going on. Over.

Dr. Portnoy: No, that's good to know. Thank you.

Dr. El Sahly: Yeah, I'm glad you pointed this point out, Dr. Weir, because the MRNA vaccines have been in phase three clinical trials for seasonal influenza. We don't have the data yet. I think I checked on clintrials.gov as early, maybe late last week and there was still nothing. But also I know these studies have been completed and their immunogenicity did not outperform the current ones. So that's why the efficacy data in the inter-pandemic period will give us at least an idea of the performance of these vaccines, hopefully pointing to a, to giving the public new options. Dr. Jódar, did I say your name correctly?

Dr. Jódar: Jódar is really the pronunciation, but they come in different ways. Thank you very much. I just like to follow up the discussions that, perhaps Dr. Portnoy, Dr. Monto and you, Dr. El Sahly have said, and perhaps, Dr. Weir can, can comment. I can just say, obviously I'm representing one vaccine manufacturers that is, also conducting clinical trials with MRNA vaccines. And yes, there is a lot of work from different manufacturers, some from different sources as Dr. Weir said.

What I just wanted to have is a clarifying question perhaps as well. And Dr. Weir perhaps, can clarify, in the graphic that is discussing the regulatory pathways for the pandemic vaccines in the pre-pandemic and the inter-pandemic period. I mean, I think it always starts with the U.S. license seasonal influence, and then you have a prototype for which you have to demonstrate safety and immunogenicity, and then you infer, effectiveness from the efficacy of the seasonal influenza vaccine. But in the guidance, also, of the FDA, there is the possibility of having an accelerated approval option. I think, and I just want to have this, clarified for those manufacturers that either do not have a U.S. licensed seasonal influenza vaccine or for new platforms, as, as we've been discussed. And here the question is whether when you, conduct immunogenicity studies, whether those antibody responses are considered an acceptable surrogate of protection. and therefore there would be an accelerated approval licensure with the commitment of a post-approval effectiveness. And I do not know, Dr. Weir, if that option is still on the table. Thank you.

Dr. Weir: So I think we've tried to make it clear many years ago, and I think we've reiterated this several times over the years, that we're open to considering other possible pathways to licensure of pandemic vaccines. The one that we have used and the one that we have outlined here again today is for us still the most straightforward way.

Other mechanisms such as what you've discussed or mentioned about using accelerated approval for a pandemic vaccine when one doesn't have a seasonal vaccine, it's still somewhat difficult because of the lack of a suitable understanding of what a correlative protection is for a pandemic vaccine. We still struggle with this for seasonal vaccines to some extent, but for pandemic vaccines there's still a gap in our understanding. Again, all I can say is we're open to considering anything that a sponsor will present to us and present the data to back it up. But that

is still the difficulty and other pathways is the data and the knowledge gaps and things like correlative protection. What is a protective mechanism? What is reasonably likely to predict? So we're open, but it's a tough area over.

Dr. Jódar: Thank you.

Dr. El Sahly: Great. Dr. Perlman.

Dr. Perlman: Yeah. I just have a question about the, some of the testing that's being done with H5N1 vaccines. So in 2014, the info, maybe a little earlier than the infamous experiments showing that, one could make a H5N1 human transmissible, by doing certain mutations in the hemagglutinin protein. This is a lot of the controversy and, prohibited certain kinds of genetic manipulations, but are those mutations that were discovered then by the Pushe and Karaoka labs, do those change the – one of those particular to change? Are they known to change the efficacy of the vaccines? Because those would be ones that would, increase binding to the two, six residues as opposed to the two, three residues.

Dr. Davis: Yeah. And, I'll start just by saying that those mutations that are identified are thankfully not changes that we have seen and circulating strains and animal reservoirs. but they're exactly the mutations that we keep an eye on to make sure that we're not seeing those. Having said that, they still remain antigenically well covered by the existing candidate vaccine viruses that have been developed. So those changes that might lead to enhanced transmissibility, and don't lead to a reduction in cross reactivity of the vaccine.

Dr. Perlman: Thank you.

Dr. El Sahly: Dr. Monto.

Dr. Monto: I'm sitting here with the discussion topics in front of me. And when I read discussion topic two, I get a little confused about what we really are supposed to be opining about. Is it possible, Jerry, to give us some possibilities of the kind of changes that might be made? It's pretty hard, with the unknown about a pandemic coming up with suggestions about proposed, new mechanisms. And I'm most concerned about those using new platforms.

Dr. Weir: Okay. So most of this discussion is not about new platforms per se, but let me give you an example. When, when we first outlined this process of using a strain change in response to a pandemic, I think most of the thinking was that one would do a prototype vaccine and do a strain change. I think we were only at the time thinking about this in a pandemic situation. So how would we rapidly respond? And all of that was well and good. And I think it served us well, but right now we're getting a lot of questions about, can we go ahead and make a strain change now, even though it's not a pandemic. And so that's why we wanted the committee's input on, does it make sense to go ahead and do this now, even though if the pandemic occurs, it might still not be the same strain. So the question for you and the other committees is, does it make sense for us to do these updates now? And I think part of the reason that it makes sense to us is because the strains that were used in the prototypes are so old now. And I think it would, as Dr. Kaslow said at the very start of the meeting, I mean, I think this adds to our data package. I think it adds to our confidence in the vaccine. And so that's why we wanted just your opinion about whether the current situation is right for updating these vaccines for preparedness purposes. And then of course, the last.

Dr. Monto: You're not talking about pre-pandemic vaccine use, which some have proposed.

Dr. Weir: We're not talking about vaccination policy or use. We're just talking about making the update to the vaccine and accumulating the CMC and the immunogenicity data to go with it

in this inter-pandemic period. Does that make sense to you? How would that differ from what's going on now with the CVVs? Well, CVVs are typically made and for the vast majority of them, not much is done, but after the CVV is made, they're not put…

Dr. Monto: So it's basically doing testing in humans?

Dr. Weir: Yes, only for a strain update, we would expect that the manufacturer makes a lot of vaccine, not just have the CVV, but make a lot of vaccine, put it into a small clinical trial, generate the immunogenicity data, as well as the CMC data to show that they can manufacture it. So these are still pretty small scale, but it is preparedness.

Dr. Monto: Well, how can anybody be against that if the mechanisms can be worked out?

Dr. Weir: Okay.

Dr. Monto: That would be my response.

Dr. El Sahly: Thank you. I have a question to Dr. Davis. I wonder if it's feasible to pull the slide where you showed the ferret antisera against, raised by different strains against the different strains, you know, that two by two, not two by two, you know which table I'm talking about. It's just that it flew past, and I couldn't focus on a couple of things I wanted to see.

Dr. Davis: Yeah, so I think this is the primary homoagglomeration inhibition assay that demonstrates the cross reactivity of the Astrakan CVV, as well as two other CVVs developed to the 2344Bs against human cases of the 2344Bs after exposure to either poultry or dairy cattle.

Dr. El Sahly: The one closest to what's circulating in cattle and birds in the U.S. would be the last one, the Texas, right?

Dr. Davis: So that's not a CVV, that is just ferret antisera produced to the wild-type virus from the first human case detected in the U.S.

Dr. El Sahly: Okay, all right.

Dr. Davis: And maybe one last point just to caution everyone in interpreting the data, you know, the higher titer doesn't necessarily mean broader cross reactivity. And so, what we're really looking at is the reduction in the titers at the bottom of the test. And so again, for most of the viruses characterized to date, and we've seen good cross reactivity for all three of these candidate vaccine viruses.

Dr. El Sahly: Okay, so the one that is now mostly in clinical trial is the Astrakan, right?

Dr. Davis: That's right, RG71A.

Dr. El Sahly: Yes, and it seems, okay, so it seems to be okay, excepting maybe for the chicken gana, but we also say that the chicken gana hasn't been circulating widely, right?

Dr. Davis: That's correct. Yeah, that group remains restricted to West Africa.

Dr. El Sahly: Okay, so as a corollary to that, and to the fact that we do not have solid correlates of protection against pandemic influenza, the avian variety, we do know that the anti-neuraminidase seem to be very predictive, or they correlate statistically even the most with disease severity, with infection, with disease itself. So what is your viewpoint on using a strain where the N is mismatched, if we are thinking that the highest likelihood is an H5N1, and what's being tested is N6 and N8?

Dr. Davis: Yeah.

Dr. El Sahly: There's a little bit of N in the vaccine, and using it with AS03 is going to boost the N responses, so we will get responses to whatever N we give, unless we're using recombinant or mRNA.

Dr. Davis: Yeah, I think when we look historically at these H5 viruses, you know, we have a lot of data, and really now decades of data to show that it's really the immune response to the hemagglutinin that's important for these H5 viruses, and we can demonstrate that by raising ferret antisera, testing that sera against these circulating strains, where we see that the HA match is really the critical component, so I think is an optimal vaccine.

The other challenge, of course, is this reassortment that I've talked about, and so one of the great and unpredictable things about influenza viruses is when reassortment happens, it can be very fast and sudden, and so because these viruses have animal hosts, it makes it even more challenging to predict when that reassortment happens, and we've seen historically that these neuraminidases get swapped out frequently, and so that's a challenge from a vaccine perspective. The HA, and especially the H5 HA, is what remains fixed in these viruses, and so I think focusing on the hemagglutinin is really the important feature of the vaccine strategy. That's my opinion, and I think I can leave it at that.

Dr. El Sahly: Happy to have others weigh in. Thanks. I definitely hear you, but just statistically, it seems that the N1 caused the most disease with the clades that we just discussed a couple of questions ago, and the most widespread dissemination in mammals and spillovers of humans now, but I mean, I know we can't have it all, maybe, the answer. Dr. Gans?

Dr. Gans: So I, like Dr. Monto, was going back to our question, particularly the second question, and I was wondering, with the collaboration with BARDA, which does seem to be

producing some of the human studies and early immunogenicity data. I'm wondering how that then also is different from going through this other process, which makes sense to have the additional data to help put different, more updated compositions into these licensed prototype vaccines. But I just wasn't clear the difference since there are these other studies that were going on, and then I wondered how versatile that is in these licensed prototype vaccines, which would obviously make it easier to then just get a production for a pandemic, which we've all been concerned about. But I just worry that, well, we'll have to continue to update the composition, how, depending on how these different viruses change over time, which seems they are, so I just wondered about the clunkiness or the finesse of doing it in this way, or relying heavily on sort of the BARDA system, which seems to already be doing some of that, but maybe in a more flexible way.

And then I also wondered, again, I just wanted to ask my, I guess, veterinary question of this group, but how -- is the vaccination of our domesticated animals feasible, or does it make sense to help stop some of the changes that we're seeing in this virus so they wouldn't replicate so widely, and is, in your knowledge, any work being done in that realm?

Dr. Oshansky: So I can comment quickly on the BARDA clinical studies, so all of the data generated from these clinical trials, that data would be integrated into the data packages that would be submitted to CBER, and so GSK's data package, CSL Securis' data package, all that safety and reaction, the safety and immunogenicity data would be incorporated into the license, the request to update the license.

Now, the Sanofi egg-based antigen with either GSK, ASO3, or CSL Securis' MF59 study, that's BARDA-sponsored study, because that's not licensed, all of that data, it's anticipated to place it into an existing pre-emergency use authorization package, so that that data, it already

exists, it's already in a pre-EUA format, so that it can be easily accessed if needed, if there were to be an emergency.

Dr. El Sahly: Dr. Rubin?

Dr. Rubin: Sorry, I was just looking at the data on neutralization, and of course the thing that jumps out in that table is that the serum induced by vaccination with the Gana chicken antigen is by far the best. How long will it be until you have that ready to go, if we needed it?

Dr. Davis: Yeah, we're hoping it's just a matter of perhaps a month, and I don't want to guess too much, but we're nearing the finish line, and so I think it's close, but still a few things to finalize before we're ready to distribute to manufacturers. I will add that, again, the titers and the comparative titers between the different CVVs, I might not put too much emphasis on that and how it translates from a ferret immune response to a human immune response. In the ferret model, we do an intranasal inoculation with relatively high titers of these Canada vaccine viruses as infectious viruses, to be sure that we generate the highest titers we can get, so I think that could be also viewed as a bit of an artifact of the model that's used.

Dr. Rubin: So you're saying that ferrets are not just very small for rear human.

Dr. Davis: That's right.

Dr. El Sahly: I guess the emphasis is on the antigenic differences, not so much the magnitude of the response, right, Dr. Davis?

Dr. Davis: Correct.

Dr. El Sahly: Okay, Dr. Wharton.

Dr. Wharton: Thank you. Going back to the questions, you know, I think that it was a very thoughtful process that was proposed a number of years ago for developing these prototype vaccines in a pre-pandemic period to enhance preparedness. It is excellent that there were a number of vaccines that were actually licensed for this use, but those vaccines are all based on much older H5 viruses that are, I think, no longer in circulation, and certainly the 2344B viruses that we are now most acutely concerned about. There are a number of candidate vaccine viruses that look good. I think the proposed process or the proposal to update the inter-pandemic process to allow those prototype vaccines to be updated, as Dr. Monto said, it's just hard to imagine any reason not to do that under the current circumstances, and even if, you know, we never have to use a 2344B vaccine, I think it would, you know, likely be a very good investment, and should we end up needing one of those vaccines in the future or something similar, I think we'd be in a much better situation by having these updated pre-pandemic vaccines during the inter-pandemic period. So I appreciate FDA asking the questions, and it seems to me that for question two, we can say yes. Thank you.

Dr. El Sahly: Thank you, Dr. Wharton. I do not see any raised hands for the points of the discussion. That was very thorough. Thank you all for the very thoughtful questions. I think the proposal is rational. The older strains are no longer circulating. We need to understand the current landscape when it comes to safety, immunogenicity, and vaccine development.

The minor proposal that I would want us to consider, and it goes kind of along the lines of what's happening in Europe, unless the people in Europe generate those data, which is there is an opportunity to understand correlates of protection from a pandemic or an avian, even if it doesn't become a pandemic because of reasons discussed during the talk today, to study the correlates of protection from avian influenza by probably moving the phase two studies to

preferentially vaccinate those at risk by virtue of, so it's like a phase 2A/2B study, to study the safety and immunogenicity in those individuals with the potential that it might give us a signal of efficacy. That would be one thing that we can utilize the current epidemic and zoonotic that is taking place to understand future approaches to avian influenza immune-vaccination. And I still am a bit concerned about the mismatch with the end, but for now, I see that the HAI remains the most important, but efforts at matching the ends as well should be considered if feasible. Dr. Oshansky.

Dr. Oshansky: Yes, thank you. I just, I did want to comment, you know, I inadvertently didn't mention it during my piece, but the clinical trials that we have ongoing, especially the one at CSL secure, the sponsored by CSL Securus, both that one and the GSK sponsored study, they did target poultry workers and those workers who are occupationally exposed to birds. So that includes zoo workers, individuals like this. So we're still waiting for the final data, but that is a component of those clinical trials. And then the BARDA clinical trial, we did, we tried to position the clinical trial sites close to the commercial poultry farms as well as the dairy cattle outbreaks. So it remains to be seen what the final data looks like, but that's, it's incorporated into some of our sub-analyses.

Dr. El Sahly: That's wonderful. Any final thoughts? Okay. Well, my question now to Dr. Weir is are you satisfied with the discussion? Are you clear on where the committee generally stands when it comes to these two questions?

Dr. Weir: I think it was a very good discussion. And I think all of us here appreciate the VRBPAC's input on these type of questions and discussion topics. And our goal is to continue to involve you at the committee and all discussions about influenza vaccines in general and certainly pandemic vaccines. So yes, we very much appreciate it. And I certainly think we did a

very good job following the discussions. And I hope you appreciate the updated information that we provided. Over.

Dr. El Sahly: Definitely. Thank you all. Okay. So that gives us 10 more minutes of break. No, first I need to turn it over to Kathleen to adjourn officially.

Topic II Adjourned

Ms. Hayes: Thank you. So we can officially adjourn topic two for today. And then we will come back in at 10 minutes. So at 1:33. Thank you, everybody, for your participation through topic two.

Topic III - Hear an Overview of Research Programs in the Laboratory of Pediatric & Respiratory Viral Diseases

Dr. El Sahly: Welcome dear committee members, participants, and the public. This is the slot for topic three, where we will be hearing an overview of research programs in the Laboratory of Pediatric and Respiratory Viral Diseases and the Laboratory of DNA Viruses and the Division of Viral Products at the Office of Vaccine Research and Review Center for Biologics Evaluation and Research. We will begin topic three with Kathleen Hayes. Kathleen.

Ms. Hayes: Yeah, thank you, Dr. El Sahly. Welcome everyone to this afternoon. For those who didn't attend the morning session, we have completed both topics one and two, and we're now beginning the open session of topic three to hear both of the laboratories that Dr. El Sahly just noted.

Roll call, Conflict of Interest Statement

The attending members for this topic include our chair, Dr. El Sahly, Dr. Berger, Dr. Bernstein, Dr. Chatterjee, Dr. Gans, Dr. Jódar, our industry representative who will be only attending the open portion of this topic. Dr. Monto, Dr. Offit, Dr. Perlman, Dr. Portnoy, the

consumer representative, Dr. Rubin and Dr. Shane, and our temporary voting member, Dr. Wharton. So for topic three, we have a total of 13 participants, 12 of which are voting and one non-voting member.

And now I will proceed with reading the FDA conflict of interest disclosure statement for the public record.

The Food and Drug Administration is convening virtually today, October 10th, 2024, for the 187th meeting of the Vaccines and Related Biological Products Committee under the authority of the Federal Advisory Committee Act of 1972. Under topic three, the committee will hear an overview of the research programs in the Laboratory of Pediatric Respiratory Viral Diseases and the Laboratory of DNA Viruses and the Division of Viral Products in the Office of Vaccines Research and Review and CBER. Our agency guidance session is determined to be a non-particular matter, which would have no impact on outside financial interests. And for topic three, no external affected firms or entities were identified and members were not screened for this topic. After the open session is completed, then be closed to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy.

And this concludes my reading of the conflict of interest statement for the public record. And I will hand it back over to our chair, Dr. El Sahly.

Dr. El Sahly: Thank you. Thank you, Kathleen. I would like now to invite Dr. Elkins. Dr. Karen Elkins is the Associate Director for Science, CBER FDA. She will give the overview of CBER research program.

Overview of CBER Research Programs – Dr. Karen Elkins

Dr. Elkins: Thank you, Dr. El Sahly. And we can move right on to the next slide. So I'd like to tell you a little bit about the intramural research program at CBER as context for your discussion of the site visit report that is the subject of topic three for today. As you all know, CBER regulates biological products. Most of these are produced by biological systems and that makes them inherently complex, as are their utilization. And so the scientific basis of regulation is clearly important.

And in fact, it's so important that CBER has always been intertwined with the research program and research that supports challenges in the development and evaluation of medical products is an explicit goal of CBER's strategic plan.

Our intramural research program is now located on the White Oak campus in Silver Spring. We have space in two large buildings that comprises about 450,000 square feet for research labs and about 425 research staff. Those are supported by a series of research core facilities, as well as a state-of-the-art bivarium. The funding for our research program comes primarily from annual congressional appropriations. There are a few targeted CBER and FDA programs and a few external grants. And our research staff is a mix of permanent principal investigators who direct independent investigator-initiated research with some permanent staff scientists, technicians, and research fellows that are typically temporary.

This model of doing business has been around since CBER's inception, affectionately called the researcher-reviewer model. We conduct investigator-initiated research, but the topics, of course, should be directly linked to the products that we regulate. So they may range the gamut from looking fairly basic to fairly applied, but they are all designed to develop data and tools that support the development of classes of products and to fill knowledge gaps, particularly

those that may inform policy development and regulatory decision-making. So research and review are integrated from the start.

CBER researchers are integrated into regulatory review teams. The most typical role for a researcher is as the so-called CMC reviewer, where the responsibility lies in assessing the scientific rationale, any data presented in support of proof of concept of a product, but especially the way in which the product is made, quality control tested, and the implications of production for its safety and efficacy. In addition, product reviewers also assess the clinical assays that may come along as part of clinical studies. And CMC reviewers are part of an overall team, which may consist of a regulatory project manager, a clinical reviewer, a farm tax reviewer, and a statistical reviewer.

So we think that doing business this way has a number of advantages. The research program develops specific knowledge and tools that support product development. But beyond those concrete outcomes, it ensures that our reviewers have a state-of-the-art understanding of techniques that are the source of data that we see in regulatory submissions. Moreover, the research program facilitates the recruitment and retention of highly trained scientists and prepares for future innovative products and public health challenges; and we just lived through a great example of that. Taken together, having the intramural research program ensures efficient, credible, and highly effective review and decisions based on sound science.

Our research is evaluated in a number of ways. We provide annual project reports. Those are reviewed by all applicable supervisors and managers. When new projects come along, there are specific efforts devoted to reviewing those before they are initiated. Each level of the center, including the center itself, as well as each office has a variety of scanning processes that may reveal new directions that should be considered as part of the research portfolio. And then the

subject of today's discussion is an external site visit by external subject matter committee members who serve to critique our research programs from a fresh point of view.

Not to bog you down in organizational details, but again, as context, CBER is divided into eight offices. An odd name, I know, but that is the organizational structure. Offices are divided into divisions, and divisions are divided into units with another odd name, a lab or a branch. Lab, in this case, meaning a group of principal investigators who work together on similar subjects. And it's at the lab or branch level, those titles are used interchangeably, that the site visit is conducted. Today, there are labs that have a small number of investigators in each, and so the site visit for them was conducted jointly.

So the site visit itself, it consists of the reviewers receiving written research reports from the investigators, hearing oral presentations, and then conducting interviews with the investigators. And that event results in an evaluation, and the criteria for evaluation include things that will be familiar to you. We ask reviewers to comment on the scientific quality and its uptake by the scientific community that is having an impact on our stakeholders. Needless to say, for the external stakeholders, the research, we expect research to be disseminated by way of publications, presentations, technology transfer activities, whatever is applicable. And we expect it to be mission relevant. We expect it to align with CBER goals, to support product development, and to provide our review capabilities.

We ask the reviewers to focus on specific things. The primary focus is on the quality and relevance of the science. The review is both retrospective and prospective. So we ask for comment on progress since the last site visit and on the quality and nature of the proposed future research directions. To the extent that reviewers notice aspects to comment on, including

laboratory organizations, program management, and mentoring skills, we also welcome that input.

The outcome of a site visit is a report from the committee. And that is what you have in front of you today. At the moment, it's considered a draft. And you have three options for disposition of the report: You may accept it as is, you may amend it yourself as a committee, or you may reject the report and send it back to the site visit committee for further work. Ultimately, you will vote on accepting the report. And the report is final only upon your approval. That final report is used in many ways. Obviously, it's a review of individual scientists' progress. But much more than that, it's used by the PIs and their research staff to improve their research programs. And it's used at all levels of supervisors and managers, both to improve the individual programs as well as to consider the overall research portfolio and to allocate resources as indicated.

So with that, I'd like to thank you very much for your review of this. The site visit itself is incredibly important in ensuring that CBER maintains high-quality research programs. And this external review really is critical to allowing our research programs to contribute directly to our regulatory mission. And I'm happy to answer any questions.

Overview of CBER Research Programs – Q & A

Dr. El Sahly: It's wonderful. Any of the committee members with a question for Dr. Elkins? First question from Dr. Rubin.

Dr. Rubin: It's not a question. It's just a comment, which is I just want to, again, salute the FDA for using this system where actual scientists are doing the review. I think it really helps us in our determinations. I think it helps the public in order to keep them safe. So thank you, Dr.

Elkins.

Dr. Elkins: Thank you, Dr. Rubin. Needless to say, we appreciate that positive comment. But I'm convinced of its value as well.

Dr. El Sahly: Thank you so much, Dr. Elkins.

Dr. Elkins: Thank you all.

Overview of OVRR & DVP Research – Dr. Tod Merkel

Dr. El Sahly: I'd like to invite now Dr. Tod Merkel, who is Associate Director for Research, Office of Vaccine Research and Review at CBER FDA. He will give an overview of the Office of Vaccine Research and Review and the vision of viral products.

Dr. Merkel: Thank you. The Office of Vaccine Research and Review's mission is to protect and enhance the public health by assuring the availability of safe and effective vaccines, allergenic products, and other related products. We regulate vaccines, allergenic products, live biotherapeutic products, and phage.

Our core activities are to review and evaluate and take action on INDs, BLAs, amendments and supplements for vaccines and related biological products. And we also participate in the inspection of manufacturing facilities. We develop policies and procedures governing the pre-market review of our regulated products. And we conduct research that's related to the development, manufacture, and evaluation of vaccines and related products and also directed to better understand pathological processes.

Our research program is designed to complement and support the regulatory mission by focusing on issues that are related to the development of safe and effective products.

The research program in the Office of Vaccines is extremely important and contributes importantly to our ability to regulate. Because our products are intended for mass use and often universal use, and because the recipients are healthy individuals and often children, we have a tremendous emphasis on safety. Our products undergo a very high level of scrutiny by the public, both by an increasing number of anti-vaccine organizations, but also organizations that are pro-vaccine and are anxious for us to approve products as quickly as possible. And because of this high level of scrutiny, our decisions have to be based on really solid science. We also have to keep pace with technology, not only the rapidly changing manufacturing technologies, but the technologies used in the research world to develop and evaluate our products. We have to respond to public health threats. Recent threats include antibiotic resistance and emerging agents. And as Dr. Elkins pointed out, we had a really recent excellent example of our ability to respond to an emerging agent. And importantly, the results that we generate in our research program are published. They're put in the public domain. So our research benefits not just individual companies, but the entire industry sector. And finally, our research program is really critical for our ability to recruit and retain expert scientists to support our review.

Our research is broad. Although we can't cover everything, we need to cover as much as possible within the scope of our regulatory responsibilities. It's collaborative. Our researchers collaborate. We collaborate with each other. We collaborate with other scientists around the country and around the world. And this allows us to leverage our investments in our research program. The quality of our research is excellent. Our research is published and broadly cited and used. Our research scientists are members of the broader scientific community, and many are well-known experts in their field.

I think importantly, our research is investigator initiated and flexible. This allows our researchers and reviewers to anticipate regulatory needs and get into the laboratory and proactively address important questions.

The Office of Vaccine Research and Review is directed by Dr. David Kaslow, and Deputy Director is Karen Bach. It consists of four divisions. Two of the divisions, the Division of Review Management and Regulatory Review, and the Division of Clinical and Toxicology Review are focused primarily on the review of regulatory submissions. Two of the divisions we refer to is our research divisions. These divisions, in addition to contributing to regulatory review, conduct research. This is the Division of Bacterial, Parasitic, and Allogenic Products and the Division of Viral Products.

The Division of Viral Products' mission is to regulate viral vaccines and related biological products to ensure their safety and efficacy for human use and to facilitate the development, evaluation, and licensure of new viral vaccines that positively impact the public health.

The DVP's major responsibilities include the review of investigational new drug applications, biological license applications, and other pre-marketing activities, the review of BLA supplements, lot release, and other post-marketing activities, manufacturer inspections, consultation with other public health agencies, and they also conduct research related to the development, manufacturing, and evaluation of viral vaccines.

The role of DVP's research is the research and laboratory activities complement the regulatory mission. They address issues related to regulated viral vaccines. They anticipate and address issues related to the development and evaluation of new viral vaccine products.

The Division of Viral Products has seven laboratories. Two of the laboratories are the subject of today's reports, the Laboratory of Pediatric and Respiratory Viral Diseases, the chief is Zhiping Ye, and the Laboratory of DNA Viruses, the chief is Keith Peden, and Dr. Ye and Dr. Peden will be presenting next.

We really appreciate your time and efforts to review the laboratories and these reports and your opinions and comments are very helpful to us and important to us, so I'd like to thank you for that and take any questions.

Overview of OVRR & DVP Research – Q & A

Dr. El Sahly: Thanks, Dr. Merkel. Please use the raise your hand function should you have any questions to Dr. Merkel. I don't see any. Thank you so much, Dr. Merkel.

Dr. Merkel: Thank you.

Overview of Laboratory of Pediatric & Respiratory Viral Diseases – Dr. Zhiping Ye

Dr. El Sahly: Next on the agenda is Dr. Zhiping Ye. Dr. Ye is chief and PI at the Laboratory of Pediatric and Respiratory Viral Diseases, Division of Viral Products, Office of Vaccine Research and Overview at CBER. He will give an overview of the Laboratory of Pediatric and Respiratory Viral Diseases.

Dr. Ye: Thank you. There are three PIs in this group. Myself, Robert Daniel, and Dr. Judy Beeler. After 35 years, Dr. Judy Beeler decided to retire and her project did not review in this period. I do want to take this opportunity to thank Dr. Beeler's service for the government.

My group, this slide shows the personnel in my group and my major regulatory responsibilities, and as you can see, just the flu, vaccines, and our area, research area, folks on the medical and genetic approach to improve influenza vaccines.

Okay. This slide shows the influenza immunomodulase, antigen, and efficacy in the vaccine team, led by Dr. Robert Daniel. He joined this group in 2019 and this slide shows the staff in his group during this time period, and some people already left. And the major regulatory responsibilities is focused on influenza vaccines and also COVID vaccines. I think the research area is focused on the improvement of the influenza vaccine by including other antigens rather than those antigens being included in the current vaccines. And as we discussed here, the NA immunomodulase is critical, and this study, research study to try to improve how to include this antigen into the vaccine to improve the vaccine efficacy.

Dr. Judy's lab did not review in this time period, but I wanted to mention that the research area is focused on the development of serological tests to measure the correlation of protection against viruses related to the respiratory infection. I think this research is pretty critical because the correlation is very important in the efficacy for clinical studies.

In addition to the research activities, we do have the responsibility in review and this slide shows the regulatory review load. And we are starting with pre-IND, usually when manufacturers or sponsors wanted to submit a new drug, a new investigation of a new drug, they usually contact us to provide the pre-IND to make sure they can provide adequate information for the IND. And once the IND comes in, then we will start to review this. And usually if we have any issues, and we have a back foot for communication, so there are quite a few amendments to make sure the original IND is adequate to be pursued. And once we have this IND, then the manufacturers decided to submit biological license applications. So the BOA will get in, and once they have a BOA, then they have some -- improve the vaccine production, and so on and so forth. So there are quite a few sublimates involved. And we're also involved in some consultation reviews, if other office needed some expertise from us.

And this regulatory review responsibilities also involved in the following, the production, the product review of the viral vaccines, which include influenza vaccines, respiratory sensitive vaccines, COVID vaccines. And also we're involved in vaccine lot release, just to make sure when manufacturers have those lots, they will be adequately being reviewed and before distributed to the market. And we're also involved in the manufacturer inspections, and also participating in vaccine advisory committee on vaccine product issues and vaccine strain selections.

And other regulatory and public health responsibilities of this lab involved in strain selection and recommendation of strains for seasonal influenza vaccines. And it's one of the WHO essential regulatory labs, and we're involved in the strain selections. And also we are involved in serological analysis of the vaccines with response to the northern and southern hemisphere strain selections. And we're also involved in antigen drift, and this is Dr. Daniel's lab involved in this project as well. And we're also in preparation of propensity reagents for testing candidate pandemic influenza viruses vaccines. And also we are involved in WHO vaccine-related guidance.

And my lab is focused on research aims as the following. The first is focused on the pandemic vaccine candidate viruses preparation. I think David has mentioned that we provide the CVV for the H5N8 AstraZeneca vaccines. And I think once even you have this vaccine candidate viruses manufactured and needed those vaccine candidate viruses to produce vaccine. And once I have the right vaccine, the vaccine formulation need propensity reagents to make sure the adequate antigen being formulated in a vaccine. I think this is very critical as we discussed earlier that potency reagents takes time, and especially for the pandemic situation, preparation of potency reagents is time consumed. And our research focus on how to prepare, how to improve

the preparation of the potency reagents, make sure that the reagents will be ready when a pandemic occurs.

And then number two, we're focused on not only the seasonal vaccines, but also the pandemic vaccines too. I think this committee mentioned that the vaccine efficacy, especially for the pandemic, our research will focus on using animal model, challenge immunize, actually currently we do have this, we're working on the immunize animal with AstraZeneca and challenging with H5N1, which is circulating in the U.S. and see how that one react or protect from animal model. So that will provide some prediction of how those vaccine behave once in a human.

And the third one, we're also involved in COVID-19 standards, just to make sure that the assay is adequate for the, if we need a string update for SARS-CoV-2.

And this slide shows the activity in Dr. Robert Daniel's lab. I think the first one is focused on how to select an adequate string, especially for the NA, because I think as Dr. David mentioned that they have a lot of resurgence between HANA, so I think to monitor NA and select NA is critical for the vaccine performance. And even for the egg-based and cell-based vaccine, even though the NA is not standardized in this vaccine, but the right matched NA in this vaccine is critical for the vaccine performance. And they also inverted an assay to make sure we can select adequate NA antigens. I think they are focused on a simple, easier method, not only can use it to just identify the NA, but also have a potential to identify the neutralizing antibody in this assay. And number two is that to develop manufacturing approach to produce a new and existing influenza vaccine that can elicitate [sic] improved NA antibody. I think this area they are focused on how to express NA antigens in their integrity, their stability. I think that is an important area to make sure if we have a NA vaccine that we can use this assay to make sure the

NA vaccine will be used to improve the vaccine efficacy. And the last one is they also focus on the other antigens rather than surface antigen of SARS-CoV-2. With that, I conclude my overviews.

Overview of Laboratory of Pediatric & Respiratory Viral Diseases – Q & A

Dr. El Sahly: Thank you, Dr. Ye. Any of the committee members with questions for Dr. Ye? Raise the hand. Function, should you have any? None? Thank you so much, Dr. Ye. Oh, there is one question. One question. And that is from Dr. Luis Jódar.

Dr. Jódar: Hi, Dr. Ye. Very impressive research agenda that you have in your lab. I was wondering whether you are also investigating sort of potential surrogates of protection for viral vaccines. I mean, one of the discussions I think this afternoon was the lack of surrogates or appropriate correlates of protection for influenza vaccines. Also, I don't think that we have really good correlates yet for COVID vaccines or for RSV vaccines. And I do not know if your group is interested in investigating this area.

Dr. Ye: Thank you for this question because it has given me an opportunity to mention about COVID vaccine. Yes, in our lab, we do use animal models to immunize with the vaccines. And then use this animal model for the challenge. Yes, we are doing that right now. And I think some advantage of this is we are using these live viruses and see how that protects against circulating viruses. There are some issues or something we have to work on is that some of the viruses are not so pathogenic in animal models. So let's give some difficult using this animal model. However, we still have opportunity to select the viruses because the different viruses may behave differently. So we are working on select the adequate challenge viruses for using this animal model.

In summary, we do use this animal model like a favorite model for flu and mouse model for the COVID. So this is our goal and our ongoing project to make sure that even though we may not have a conclusion of the quality of protection, but still we will provide some predictive information whether the vaccine will and how the vaccine will behave in humans.

Dr. Jódar: Thank you.

Overview of Laboratory of DNA Viruses – Dr. Keith Peden

Dr. El Sahly: Thank you, Dr. Ye. To give us an overview of the laboratory of DNA viruses, I want to invite Dr. Keith Peden. Dr. Keith Peden is chief NPI of the laboratory of DNA viruses. Dr. Peden.

Dr. Peden: Okay, thank you. So my challenge is to give you a summary of what the lab of DNA viruses is and give you a bit of its history. So LDNAV was established in 1988. Andrew Lewis was appointed lab chief in 1997, and I was appointed lab chief in 2011. LDNA was last reviewed in 2018. And while the lab was set up to review and study DNA viruses as vaccines or vaccine-vectored vaccines, its role has evolved to encompass other viruses and cell substrate safety issues as priorities change and emergencies arise. I think you heard about that from Karen and from Tod.

So changes in personnel: Haruhiko Murata was a PI, and he left in 2021 for a position in industry. He subsequently left industry and went back to the federal government.

Phil Krause, a PI, retired from FDA in November 2022 and is now an independent consultant. His personnel were transferred to me.

Andrew Lewis retired in May 2024, and Jason Gorman was recruited as a PI in 2023.

And the current organization is presented on this slide. There are three units in the lab of DNA viruses. The unit of viral gene expression, PI Jerry Weir. My unit is the unit of cell biology and molecular genetics, and Jason Gorman's unit is of structural vaccinology. And the personnel in the groups are shown here. So our regulatory responsibilities in the Office of Vaccines Research and Review has the regulation of prophylactic vaccines against bacterial and viral diseases. The Division of Viral Products has responsibility for prophylactic vaccines against viral diseases. And the lab of DNA viruses has major responsibility for vaccines against diseases originally caused by DNA viruses, and now DNA viruses as vaccine vectors for other diseases. And this is done in collaboration with other labs in DVP. We also got involved with messenger RNA vaccines as did other labs in DVP. And Jerry Weir's lab is involved in influenza vaccines and also COVID vaccines.

So the types of vaccines that we regulate, of course, are the whole gamut, viral vaccines, live attenuated and inactivated, viral vectored vaccines, subunit vaccines, recombinant protein vaccines, virus-like particles, DNA vaccines, and messenger RNA vaccines.

So in DVP, as Dr. Ye presented, we regulate all stages of development of viral vaccines, pre-INDs, INDs and amendments, master files, BLAs and their supplements, post-marketing commitments, and lot release testing and evaluation. So some recently licensed vaccines over the years, Herpes zoster vaccine was licensed in 2006, HPV quadrivalent vaccine in 2006, ACAM 2000 for smallpox vaccine, the live attenuated vaccine is in 2007, HPV bivalent vaccine recombinant, another company was licensed in 2009, adenoviral type 4 and type 7, live attenuated, this is used for the military and that was licensed in 2010. Influenza vaccines inactivated trivalent seasonal was an MDCK cell produced, was licensed in 2010 and that was

the first time an influenza vaccine produced in a tumorigenic cell substrate, the MDCK cell substrate was licensed.

The 9-valent HPV vaccine was licensed in 2014, the shingles vaccine was licensed fairly recently, and then Jynneas, which is the MVA Bavarian Nordic vaccine, a live and non-replicating smallpox vaccine, and also for mpox was licensed in 2019. Recently, the CHIKV vaccine produced in vero cells was licensed and COVID-19 vaccines, EOA approved, EOA and approved, as you know, from 2024. And recently, an RSE vaccine and messenger RNA vaccine in lipid nanoparticles was licensed in 2024.

So how does our research help the public health? We provide guidance and industry in all aspects of vaccine development and manufacturing. We develop reagents and assays to assist in sponsors in pandemic preparedness for pandemic influenza and for COVID vaccine and Jerry Weir's lab is mainly involved with that. Exploring the use of poxvirus vectors has shown very good promise, and Jerry is involved in that too.

Andrew Lewis and I, we started to address the safety issues associated with vaccine cell substrates. And we looked at the issues about residual cell substrate DNA in vaccine, and also determining whether understanding the mechanism of tumorigenesis assists in estimating risks associated with using tumorigenic cells for vaccine manufacture. In fact, the VRBPAC in 2012 was devoted to this subject.

We also, in our group, established high-throughput micro-neutralization assays against human pathogenic viruses. And Jason's lab has brought a new technology to the DVP, in fact, to CBER in general, using structural data from cryo-electron microscopy to determine antibody-antigen interactions. And this is designed to examine and defining the humoral immune

responses to natural infections and vaccinations at an atomic level with the aim of designing, evaluating, improving, and regulating viral vaccines. And in detail in the epitopes of protective antibodies combined with large-scale sequence data to aid in predicting potential pitfalls or escape pathways of vaccines.

And finally, our lab activities allow us to participate in WHO international collaborative studies to identifying binding and neutralizing antibodies for infectious diseases. And some of those over the past have been involved with influenza virus, Zika virus, LASV virus, and a study by WHO is proposed to look at binding and neutralizing antibodies for the MPOX. Their reagents are accumulating now and that study will begin when they distribute those reagents.

So that's a summary of our lab. And thank you for your attendance and attention. Thank you. Any questions, I'll be attempting to answer them. Thank you.

Overview of Laboratory of DNA Viruses – Q & A

Dr. El Sahly: Thank you, Dr. Peden. Questions from the committee? I don't know if you can help with that question, I guess, because you mentioned MPOX. And are there now, I know for the longest time smallpox antigen, whether it's the vaccinia virus or the actual vaccine, the MVA virus, were used as the antigenic, the antigen to gauge responses to the vaccine. And there were some issues with using MPOX antigens as a vaccine to measure vaccine responses, I should say, or infection, post infection. Where does the research stand now? Maybe not in your lab, but generally speaking, are we any closer to understanding the immune responses to the vaccine with the MPOX being the antigen, the antigenic source?

Dr. Peden: Yeah, I think that's a little bit out of my knowledge in depth. Dr. Weir has more immediate knowledge on pox viruses. Jerry, do you want to add comments to that?

Dr. El Sahly: If it's out of people's research or knowledge, it's fine. I apologize. I just was prompted by your slides.

Dr. Peden: No, well, the assay that we developed, we have a neutralization assay for MPOX using a high throughput assay using an MVA as the target virus. Dr. Weir's lab has a plaque reduction neutralization test. So we have assays to monitor neutralizing antibodies in our groups. I'm not quite sure about all the antigens that you're referring to in your question. I apologize.

Dr. El Sahly: Well, they're different viruses, meaning a lot of it is measured by responses to the smallpox or vaccinia or MVA, but not necessarily MPOX. So that was my question. If Jerry can answer, it's fine. If not, we'll await additional data from somewhere. Dr. Perlman.

Dr. Perlman: Yeah, I was just curious with the cryo-EM. Is that now available for use by Dr. Gorman? I thought there was a period of time when it was being set up.

Dr. Peden: No, yes, you're right. There was some structural modifications that had to be done to the building. The microscope is now in the room. I'm not quite sure whether it's operational right now, but it's getting very close to being. So we should be seeing some from data quite soon from Jason.

Dr. El Sahly: That's great to know. Additional comments or questions? Dr. Peden? None? I see no hands. Thank you so much, Dr. Peden.

Dr. Peden: Thank you.

Open Public Hearing

Dr. El Sahly: So there's a break on the agenda followed by open public hearing, followed by a break. So there are no registrations for the open public hearing session. So effectively, we can

say that this ends the open public hearing session. And there will be now a 15-minute break. 15 minutes will put us right at, let's say, 2:40.

Ms. Hayes: Yes. So the open session has now concluded. So before we move into the closed session, I just wanted to thank all speakers, participants in both topic one and topic two. So at this point in the agenda, only voting members and the temporary voting member along with FDA leadership should stay connected. So speakers, PIs, industry representative, you can feel free to disconnect. And we will be back following the break for the closed session. Thank you.