FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
168th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

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

ATTENDEES

COMMITTEE MEMBERS	
Hana El Sahly, M.D. - Chair	Baylor College of Medicine
Paula Annunziato, M.D.	Merck
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases; Centers for Disease Control and Prevention
Hayley Gans, M.D.	Stanford University Medical Center
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
Myron Levine, M.D., D.T.P.H., F.A.A.P	University of Maryland School of Medicine
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H., FIDSA	Seattle Cancer Care Alliance
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine & Children's Healthcare of Atlanta
Paul Spearman, M.D.	University of Cincinnati School of Medicine
Geeta Swamy, M.D.	Duke University
TEMPORARY VOTING MEMBERS	
Jay Portnoy, M.D.	Children's Mercy Hospital, Kansas
David Wentworth, Ph.D.	Centers for Disease Control and Prevention
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Marion Gruber, Ph.D.	Food and Drug Administration
Monica Young, Ph.D.	Food and Drug Administration
Philip Krause, M.D.	Food and Drug Administration
CDR Valerie Marshall, M.P.H., P.M.P.	Food and Drug Administration
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Prabhakara Atreya, Ph.D.	Food and Drug Administration
Kathleen Hayes, M.P.H.	Food and Drug Administration
Michael Kawcynski	Food and Drug Administration
Monique Hill, M.H.A.	Food and Drug Administration

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TOPIC I - OPENING REMARKS: CALL TO ORDER

MR. MICHAEL KAWCYNSKI: Good morning and welcome to the 168th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. We are ready to get started. Today, just like normal, I am Mike Kawcynski. I will be periodically jumping in in the meeting to make sure it runs smoothly. Today, our chair is Dr. El Sahly. Dr. El Sahly, are you ready to get started?

DR. HANA EL SAHLY: I am. Thank you, Michael. Good morning everyone and I want to welcome the members of VRBPAC, the participants, and the public for the 168th meeting of VRBPAC during which we will have two topics, first a presentation of the Laboratory of Bacterial Polysaccharides, Division of DBPAP, site visit review. The second topic will be the strain selection for the influenza virus vaccine 2022, southern hemisphere.

I want to remind everyone to use their raise

your hand function on your Adobe Connect and turn your camera on when you are asking a question or providing a comment on the presentation. This way I can tell who's in order asking for a comment, and we will take it from there. Next on the agenda is Kathleen Hayes who will do some administrative announcements.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, CONFLICT OF INTEREST STATEMENT

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. My name is Kathleen Hayes and it's my pleasure to serve as the Designated Federal Officer for today's 168th VRBPAC meeting. On behalf of the FDA, the Center for Biologics Evaluations and Research, and the Committee, I would like to welcome everybody to today's virtual meeting. As Dr. El Sahly stated, the meeting will have two topics, topic one, to here an overview of the research program in the Laboratory of Bacterial of Polysaccharides within the Division of Bacterial, Parasitic and Allergenic Products, and then our second

topic, to make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2022 southern hemisphere influenza season.

Today's meeting topic was described in the Federal Register Notice that was published on August 24th. Now, I would like to acknowledge the contributions of a few other members of the DSAC team, including our director, Dr. Prabhakara Atreya, Ms. Monique Hill, Dr. Jeannette Devine, and Ms. Christina Vert, who assisted in preparing for this meeting. I would also like to express my thanks to Mr. Mike Kawcynski for facilitating the meeting today. For any media or press-related questions, you may contact the FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles.

We're going to begin our meeting by taking a formal roll call for the committee members and temporary voting members. When it's your turn, please turn on your video camera and unmute your phone and

then state your first and last name, your expertise, and your organization. When finished, turn off your camera and we'll proceed to the next person. Please see our member roster slide in which we'll begin with our chair, Dr. El Sahly. Dr. El Sahly, go ahead.

DR. HANA EL SAHLY: Morning everyone. Hana El Sahly, Baylor College of Medicine. I am in the department of molecular virology and microbiology. I (audio skip) work centers and clinical vaccine (audio skip).

MS. KATHLEEN HAYES: Thank you. Dr. Cohn.

CAPT AMANDA COHN: Good morning everyone. Dr. Amanda Cohn. I'm with the National Center for Immunization and Respiratory Diseases. I am a pediatrician with expertise in vaccine policy.

MS. KATHLEEN HAYES: Thank you. Dr. Shane.

DR. ANDREA SHANE: Good morning. My name is Andrea Shane. I am at Emory University and Children's Healthcare of Atlanta. I am in Pediatric Infectious

Diseases and my area of expertise is in the study of infectious diseases in children. Thank you.

MS. KATHLEEN HAYES: Thanks. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning. My name is Archana Chatterjee. I am the dean of Chicago Medical School and Vice President for Medical Affairs at Rosalind Franklin University. I'm a pediatric infectious diseases specialist with expertise in vaccines. Thank you.

MS. KATHLEEN HAYES: Thank you. Dr. Meissner.

DR. H. CODY MEISSNER: Good morning and thank you. My name is Cody Meissner and I'm a Professor of Pediatrics at Tufts Children's Hospital in Boston.

MS. KATHLEEN HAYES: Thank you, Dr. Meissner. Dr. Swamy.

DR. GEETA SWAMY: Good morning. Geeta Swamy. I'm a Professor of Obstetrics and Gynecology at Duke University.

MS. KATHLEEN HAYES: Thank you. Dr. Gans.

DR. HAYLEY GANS: Good morning. Dr. Hayley Gans, pediatric infectious disease at Stanford University. I do research (audio skip).

MS. KATHLEEN HAYES: Thank you. Dr. Janes.

DR. HOLLY JANES: Good morning. I'm Holly Janes. I'm a professor (audio skip) --

MS. KATHLEEN HAYES: You're coming in a little quiet, Dr. Janes.

DR. HOLLY JANES: Okay.

MS. KATHLEEN HAYES: That's better.

DR. HOLLY JANES: Is this better?

MS. KATHLEEN HAYES: Yeah.

DR. HOLLY JANES: Okay. Thank you. My name is Holly Janes and I'm a Professor of Biostatistics at the Fred Hutchinson Cancer Research Center. I work in vaccine evaluations and HIV (audio skip).

MS. KATHLEEN HAYES: Thank you. Dr. Portnoy.

DR. JAY PORTNOY: I'm Dr. Jay Portnoy. I'm a Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine and an allergist/immunologist at Children's Mercy Hospital in Kansas City.

MS. KATHLEEN HAYES: Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Good morning. Michael Kurilla. I'm the Director of the Division of Clinical Innovation at the National Center for Advancing Translational Science within the National Institutes of Health. I'm a pathologist by training and a background in infectious disease product development including vaccines.

MS. KATHLEEN HAYES: Thank you. Dr. Levine is going to be joining us for the second topic and so is Dr. Annunziato. We're going to move onto Dr. Spearman.

DR. PAUL SPEARMAN: Hi, I'm Paul Spearman. I'm Director of Infectious Diseases at Cincinnati

Children's Hospital. I direct a basic science laboratory working on HIV and other viruses. I work in the area of clinical trials of vaccines. Thanks.

MS. KATHLEEN HAYES: Thank you. Dr. Offit.

DR. PAUL OFFIT: Good morning, I'm Paul Offit. I'm a Professor of Pediatrics in the Division of Infectious Diseases at Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. My expertise is in the area of vaccines.

MS. KATHLEEN HAYES: Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Thanks Kathleen. I'm Steve Pergam. I'm an associate professor at Fred Hutchinson Cancer Research Center in Washington, infectious disease (audio skip) adult physician by training. My specific focus is (audio skip) infections (audio skip).

MS. KATHLEEN HAYES: Thank you. Dr. Wentworth is also going to be joining us for topic two. He will be a temporary nonvoting member for today. Thank you all the committee members for your introductions. I

also wanted to verbally acknowledge CBER leadership and management, including Dr. Marks, Dr. Witten, Dr. Young, Dr. Gruber, Dr. Krause, Dr. Chumakov, Dr. Slater, and Dr. Burns, some of who will be joining the meeting later today, and others who will presenting during the first topic of our meeting.

Before we begin with the Conflict of Interest Statement, I wanted to remind everybody with our virtual format to please keep yourself on mute to avoid feedback. Then, if you have your hand raised and are called upon to speak by Dr. El Sahly, please speak slowly and clearly so that your comments are accurately recorded for transcription and captioning. I will now proceed with reading the first Conflict of Interest Statement.

The Food and Drug Administration is convening virtually today, September 30th, 2021, for the 168th 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, from Baylor College of Medicine, is serving as the

chair for this meeting today for both topic one and topic two. With the exception of the industry representative member, all standing and temporary voting members of our PAC our appointed Special Government Employees or Regular Government Employees from other agencies. They're authorized to participate in closed sessions when they are held.

Dr. Paula Annunziato, of Merck, will serve as the industry representative to this committee. Industry representatives act on behalf of all related industry and bring general industry perspectives to the committee. However, industry representatives are not appointed as special government employees and serve only as nonvoting members of the committee. They are not authorized to attend any closed sessions, therefore, industry representatives are expected to leave when the open sessions end.

Dr. Jay Portnoy is serving as the temporary consumer representative for this committee. Consumer representatives are appointed Special Government Employees and are voting members of the committee and,

hence, do have voting privileges and they do participate in the closed sessions when they're held. The meeting today will have two Conflict of Interest Disclosure Statements read prior to each topic session that will occur during the meeting.

For topic one, the following information on the status of this committee is compliant with federal ethics and conflict of interest laws, including but not limited to 18 USC Section 208, is being provided to participants in today's meeting and to the public. In the morning today, September 30th, 2021, under topic one, the VRBPAC committee will meet in open session to hear overview presentations on the research programs conducted in the Laboratory of Bacterial Polysaccharides, Division of Bacterial, Parasitic and Allergenic Products, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research.

Per agency guidance, these sessions are determined to be non-particular matters which would have no impact on outside financial interests, hence, no affected firms are identified and members are not

screened for this topic. After the overview presentations are completed in the open session, the meeting will be closed from 10:45 a.m. to 11:45 a.m. to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy.

We would like to remind members and consultants that if they have any personal or professional conflicts with any individuals that are subject to the closed meeting deliberations, then participants need to inform the DFO and exclude themselves from such involvement. Their exclusion would be noted for the record. This concludes my reading of the first Conflict of Interest Statement for the public record. I would like to hand it back over to Dr. El Sahly. Thank you.

DR. HANA EL SAHLY: Thank you, Kathleen. We Will begin presentations this morning with Dr. Monica Young. Dr. Monica Young is senior advisor to the associate director for research at the FDA. I want to remind you, Dr. Young, to turn on your camera, unmute your phone, and we are all ears.

OVERVIEW OF RESEARCH/SITE VISIT PROCESS, CBER

DR. MONICA YOUNG: Thank you, Dr. El Sahly. In the next few minutes, I will give an overview of the CBER research program, including how the research program is evaluated and how site visit reports are used. CBER regulates a number of complex products, including blood and blood products, cell and gene therapies, tissues, vaccines, therapeutic probiotics and over 400 allergenic products. CBER has scientists with broad areas of expertise to cover the variety of topics and challenges that arise when regulating biologics.

Here on this slide are four main goals of CBER's current strategic plan to support CBER's mission and advance the scientific basis for regulation of biologics, human tissues and blood. Goal two is conducting biologics research with the goal to conduct research to address challenges in the development and regulatory evaluation of medical products. CBER takes

a collaborative approach to regulating biologics including review of data submitted by sponsors, internal discussions, post-market surveillance and active research.

The research programs are investigator initiated and range from basic to targeted studies related to regulated products. The research program helps to ensure understanding of advance techniques that are the source of data in regulatory decisions. The research program helps to ensure efficient, effective, and credible review and fosters regulatory decisions based on science. CBER's research and review are integrated. What I mean by this, is that a regulatory review team in CBER includes a chemistry, manufacturing and control, or CMC, product reviewer who evaluates aspects of the submission, such as scientific rationale, data for proof of concept, production techniques and resulting product, quality control testing and clinical assays.

Some of the CMC product reviewers are what we call researcher-reviewer. A researcher-reviewer review

regulatory submissions and lead research programs. This schematic demonstrates how CBER's research programs fills gaps in scientific knowledge and helps to overcome obstacles in product development. As the public health needs arise, novel products are needed and come with regulatory challenges. Some of these challenges include major questions such as how best to characterize complex products or how best to design non-clinical studies to provide predictive assessment of safety and efficacy and how to overcome potential contamination of biologic products.

This is where we apply science to developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA regulated products. The discovery of new tools assist in regulatory policy and decision making. The outcome of regulatory science provides improved data to assess the benefit and risk ratio of products and in many cases leads to the licensure of novel biologics.

Currently, CBER's core research facilities include flow cytometry, confocal and electron

microscopy, a high-performance integrated virtual environment we call HIVE, which provides bioinformatic support for next-generation sequences analysis. We have a biotechnology core facility with state-of-the-art instrumentation as well as a vivarium and biosafety-level-three laboratory.

CBER is active in leveraging resources and fostering collaborations. This chart shows you the type of formal collaboration for FY21. CBER has collaborations nationally, internationally and across sectors within the government and within the agency as well. The pie chart shows the formal external leveraging mechanisms that were used this year. It ranges from Confidential Disclosure Agreements all the way to Employee Invention Report. There are many benefits to the CBER research program.

The research program allows scientists to prepare for future innovative products and public health challenges as well as develop tools and data that are available to all stakeholders and support development for product classes. The research program

attracts and maintains highly trained scientists with necessary expertise to review regulatory submissions, and the studies conducted fill knowledge gaps that inform policy development and regulatory decision making.

Now we'll look at how office management and CBER leadership evaluates research programs. Management review includes the annual review of research of a program at the project level, in addition to horizon scanning, which is done by the offices in the Regulatory Science Council, we refer to as the RSC. The Regulatory Science Council is composed of leadership across the center. External review of the research programs are conducted every four years in the form of site visits.

CBER's evaluation framework includes mission relevance -- this takes into account the alignment with similar office goals and objectives -- dissemination, which includes presentations and publications; impact -- this is the impact that that program has on scientific community and regulated stakeholders.

Lastly, unique contribution to regulatory practice. This is to evaluate the scientific outcomes of the research program and how it enhances CBER's regulatory mission. Over the last few years we have developed tools to track components that make up the evaluation framework.

Site visit review teams are subcommittees to the advisory committee. I want to thank the chair for your leadership. The draft report of the site visit has been distributed to the advisory committee. The advisory committee will accept, amend or reject the report and send back to the site visit team. Once approved by the full advisory committee, the final report is very valuable and is used in many ways. It's used by PIs for improving the research programs, by supervisors for internal review of the program's progress, and by management where resource allocation decisions may be impacted by the report.

I want to thank everyone on the site visit review team for writing the report and entities for evaluating the report. Thank you and with that I will

stop here for any questions.

DR. HANA EL SAHLY: Thank you, Dr. Young. I turn to my colleagues. Should anyone have a comment or a question for Dr. Young, please raise your hand. No raised hands. Maybe I'll begin.

Briefly, how did the structure that you just described serve CBER, I guess, during the Pandemic? Probably a lot of realignment and adjustments had to be made. Does the structure allow itself for efficiency during this pandemic?

DR. MONICA YOUNG: Could you elaborate on what you mean by structure?

DR. HANA EL SAHLY: The review, the horizon scanning, the project reviews, the structure of changing gears that does research.

DR. MONICA YOUNG: How was that affected by the pandemic?

DR. HANA EL SAHLY: Yeah.

DR. MONICA YOUNG: Yes, so there were several labs affected during the pandemic, of course, that had to stop, actually, a lot of their research for at least

six months. There were some of the COVID-related research that was able to continue, but the review still proceeded. We still went through our annual reporting. We were able to get the lab started back up, and now we're at a better place. I would say that there was definitely an impact. We didn't have site visits for the year 2020 after March 16th. There was a bit of an impact, but I do see things are slowly getting back to normal.

DR. HANA EL SAHLY: Thank you, Dr. Young for the overview. Next, I want to introduce Dr. Jay Slater, who is the director of the Division of Bacterial, Parasitic and Allergenic Products at OVRR at the FDA. Dr. Slater, please turn on your -- there you go.

OVERVIEW OF THE OFFICE OF VACCINES RESEARCH AND REVIEW (OVRR) & OVERVIEW OF THE DIVISION OF BACTERIAL, PARASITIC AND ALLERGENIC PRODUCTS (DBPAP)

DR. JAY SLATER: Thank you so much for giving

me the opportunity to speak today. Just to clarify, it's my job to transition from the previous presentation's background about the Center for Biologics Research Program and the next presentation that you'll be hearing from Dr. Vann about the Lab of Bacterial Polysaccharides. I am the Director of the Division of Bacterial, Parasitic and Allergenic Products. I'll be talking today about both the Office of Vaccines, which is above me and about my division.

Let's go ahead and talk about what OVRR regulates. You all know this. We regulate vaccines, allergenic products, live biotherapeutic products, including both probiotics and fecal microbiota for transplantation, as well as bacteria phage. It's a pretty broad pallet that OVRR regulates. OVRR's mission is to protect and enhance the public health by assuring the availability of safe and effective products within our purview.

The OVRR, obviously the core activity is to review, evaluate and take appropriate actions on INDs, BLAs, amendments, supplements for vaccines and related

products, and to participate in inspections. We also develop policies and procedures governing the premarket review of regulated products, and we conduct research related to these products. The OVRR research mission is designed to complement and support the regulatory mission by focusing on issues related to the development of these safe and effective products.

Here is an organizational chart of the Office of Vaccines. As you know, Drs. Gruber and Krause are the Director and Deputy Director of the Office of Vaccines. Within the Office of Vaccines, there is the Division of Vaccines and Related Product Applications run by Dr. Doran Fink and Dr. Loris McVittie, which is responsible for administration of these applications and, in large measure, the clinical review. Then we have two so-called research divisions.

The Division of Viral Products and the Division of Bacterial, Parasitic, and Allergenic Products, or as one of my colleagues once called it, we are the division of not-viral products. Again the research goals are laid out here. Research goal number

one is to enhance the safety of the preventative vaccines. Research goal two is to improve the effectiveness of the vaccines through the development of models. Research goal number three is to enhance the availability of those vaccines.

For this group, I think it's an obvious point, but I really want to emphasize the importance of research and the regulation of vaccines and related products. It's important that the FDA itself do research. That comes from several different reasons. One is the emphasis on safety and vaccines. Obviously, these are products for mass use, often universal use. The recipients are healthy individuals typically, often children. It's extremely important that we, in particular, be on the cutting edge of research involving safety of these products.

Again, obvious to everybody here, but there are new manufacturing technologies that are rapidly evolving. It's really important that our reviewers keep pace with that technology. There's an extremely high level of scrutiny by the public. These regulatory

decisions that we make have to be based on science. An increasing number of anti-vaccine organizations and groups are adding to that scrutiny. It really makes it critically important that on our review teams we have active scientists who really can understand and interpret the available science in the best way possible.

Obviously, we have to be nimble. We have to respond to public health threats, antibiotic resistance, C-diff, emerging adventitious agents. We want to keep all of our research results in the public domain. It's really a key principle here that we expect our research efforts to be published, to be publicly available, to be to the full benefit of the American public. Our research is broad, it's collaborative, it is investigator-initiated. This is the key aspect of our research efforts.

We do expect it to be excellent. It's one of the reasons that we are such strong supporters of the site visit program. We expect to be flexible. That will allow rapid adaptation to regulatory needs. As

such -- and you just heard about this -- we do have this research-regulator model where we integrate our researchers into product review. Out of a hundred or so people in my division, we do have a certain percent that are only doing research and not doing any regulatory work. I would say half to two-thirds of the people in my division who are researchers also do regulatory work.

Now I'm going to turn to my division, Division of Bacterial, Parasitic and Allergenic Products. I'm the director. Dr. Drusilla Burns is the deputy director. We have four labs within the division. The Lab of Bacterial Polysaccharides, which you see here on the upper left-hand corner, is the one that you're going to be discussing in greater detail today. There are three other labs, the Lab of Respiratory and Special Pathogens, the Lab of Mucosal Pathogens with Cellular Immunology, and the Lab of Immunobiochemistry.

We're going to discuss all of these labs very quickly in the next few slides. It's useful to discuss what our different labs do in terms of our overall

research-regulatory portfolio in DBPAP. This is a list and it's by organisms rather than by specific scientific areas. This is not a perfect way to represent what we do, but it'll work pretty well for the next few slides at least. You're all aware we regulate products based on non-invasive toxin producers that are listed here, including bacillus anthracis, Bordetella pertussis, the various clostridium species and Corynebacterium diphtheriae.

We also regulate vaccines and other products based on invasive organisms with a protective response to polysaccharides, certainly to a large extent H. flu and strep pneumoniae, to a somewhat lesser extent with Neisseria meningitidis, although it's still an important response. We regulate investigative products and licensed products for the intracellular organisms listed here. Increasingly, products having to do with enteric infections, parasitic infections -- although of course this is all investigational only -- and other emerging threats: staph aureus, allergenic products, live biotherapeutic products, and microbiome-related

products.

To break this down and leave this slide up, just changing color patterns, the Lab of Respiratory and Special Pathogens really focuses largely on these toxin producers. To a lesser degree, they participate in our division-wide effort in studying responses to staph aureus. The Lab of Mucosal Pathogens and Cellular Immunology focuses largely on the intracellular organisms and the enteric organisms.

It participates in the review and research of staph aureus-related products and is involved in investigational work with malaria, live biotherapeutic products, phage, microbiome-related products, as well as products aimed at C. diff. Finally, the Lab of Immunobiochemistry, which on this slide only has representation for its involvement with allergenic products. This is the lab that I'm a member of.

Frankly, it's one of the weaknesses of this way of representing it. There are over 1,200 varied allergenic products. Most of them are not standardized, which actually makes them very, very

difficult to regulate. There are a number of newer products that are out there that are coming along with a wide variety of technology. This is a very busy lab indeed from both a regulatory and a research point of view.

Finally, the Lab of Bacterial Polysaccharides, which you will be reviewing today. They are involved with largely products aimed at H. flu, meningococcus, and strep pneumoniae, as well as some work involved with plasmodium. That's not a major focus of their work. The site visit, when it last heard from all five principle investigators in the division and heard from four staff scientists or staff fellows who work under the principle investigators (audio skip).

Again, I'd like to thank the site visit committee for their thorough review and for their commitment and time both on the day of the site visit and in the weeks and months afterwards putting together the site visit report. We really value what you have to say. We take it to heart. We do implement it in terms of our guidance to the principle investigators

and the lab chief. I really wish to extend a full thanks to the site visit committee and to the entire advisory committee for considering these issues. I'm happy to take any questions.

DR. HANA EL SAHLY: Thank you, Dr. Slater. I see Dr. Cody Meissner has a question. Dr. Cody Meissner, please turn on your camera and your phone.

DR. CODY MEISSNER: Thank you, Dr. El Sahly and thank you, Dr. Slater, for that overview. One question I had relates to Borrelia burgdorferi. I didn't see that listed on your slides. I'm thinking particularly about the current study of monoclonal antibodies with a long half-life, for example. Is that something that will fall into your purview?

DR. JAY SLATER: Thank you for that question. Yeah, we should probably put Borrelia burgdorferi back on the list and indicate what role it plays on our regulatory efforts. That said, we are not involved in the direct review of monoclonal antibody products. That's a different part of the agency. We, however, would be focused on any investigational vaccine efforts

in that direction. Yes, I think point well taken. It should be on the list.

DR. CODY MEISSNER: Thank you.

DR. HANA EL SAHLY: Any other questions from the committee members?

MR. MICHAEL KAWCYNSKI: As a reminder to all committee members just in case you forgot, at the top of the screen is the Raise Your Hand option. That's how we will determine how we call on you.

DR. HANA EL SAHLY: I see no raised hands. With that, I want to thank you again, Dr. Slater, for this overview. I want to welcome Dr. Willie Vann. Dr. Willie Vann, please turn on your camera and your phone audio. Dr. Willie Vann is the chief of the Laboratory of the Bacterial Polysaccharides. He will provide an overview of the lab. Take it, Dr. Willie Vann.

OVERVIEW OF THE LABORATORY OF BACTERIAL POLYSACCHARIDES

DR. WILLIE VANN: Good morning. My name is Willie Vann. I'm chief for the Laboratory of Bacterial

Polysaccharides. The Laboratory of Bacterial Polysaccharides investigates the biochemistry, biology and chemistry of virulence factors of encapsulated bacteria. These basic research fields are related to the regulatory activities of the Laboratory of Bacterial Polysaccharides, which include but are not limited to review and approval of biological license applications and IND submissions related to vaccines against encapsulated pathogens, evaluation of manufacturing and changes in manufacturing, and on-site inspections and technical meetings with the manufacturers.

The Laboratory of Bacterial Polysaccharides also serves as a CBER resource for expertise in glycobiology, as exemplified by cross-cutting collaborations such as glycosylation of viral vaccines. The laboratory currently consists of six research programs managed by six principle investigators. Five of these principle investigators were reviewed at the last site visit. The sixth was not reviewed because that person was in the laboratory less than a year

before the site visit. I'll come to that principle investigator later.

There were five research groups that were reviewed, one cellular immunology. The principle investigator there is Dr. Mustafa Akkoyunlu who looks at the interaction of carbohydrate antigens with the immune system, addressing such questions as why infants respond poorly to polysaccharide vaccines and how that can be improved. Dr. Margaret Bash is the principle investigator for the molecular epidemiology group, looks at the role of non-capsular antigens in protection.

Some of these noncapsular antigens are now components of vaccines against meningococcus group B. Dr. John Cipollo is the principle investigator of the vaccine structure group. This studies the role of glycoconjugates in host pathogen interactions using mass spectrometry. For example, he's one of the groups who characterizes glycosylation of viruses in viral vaccines. The structural biology group and the principle investigator there is Dr. Daron Freedberg.

He studies the structure and the conformation of capsular polysaccharides with the objective of actually understanding what the immune system sees when it sees a polysaccharide or a carbohydrate-based vaccine.

The glycobiology group, which I'm the principle investigator, we study the biosynthesis of capsular polysaccharides as a toolbox for developing betters ways of manufacturing and analyzing capsular polysaccharide-based vaccines. Since we are research and reviewers, during this review period we have had several major accomplishments. These major accomplishments require many months of review by a multidisciplinary team.

In 2018, we were part of the team that licensed Vaxelis, which imposed diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, inactivated polio, haemophilus b conjugate, and hepatitis B recombinant vaccine. In 2020 we licensed a new meningococcal tetravalent glycoconjugate vaccine. In 2021 we were reviewing two original biological license applications for the licensure of two new

vaccines. These were new vaccines against strep pneumonia. Subsequent to the site visit, these vaccines have now been licensed.

In addition to these major accomplishments, we had several other things that we've done during this four-year review period. We reviewed hundreds of IND submissions. We have reviewed and approved over 200 biological license application supplements. These are supplements that actually relate to changes in manufacturing which actually have to be reported to the agency. The laboratory is organized to address existing issues related to vaccines against encapsulated pathogens and in anticipation of issues arising from the evolution and growth of glycoconjugate vaccines based on technological advances.

In the next slide is a historical and future trajectory of polysaccharide vaccines to give you an example of what we mean by evolution. The first polysaccharide-based vaccines were pure polysaccharides, and that was back prior to the '80s and up to the '80s, where the polysaccharide purified

from the bacteria was used as a vaccine. It worked in adults with short-term protection but did not work in infants. Based on knowledge of the immunology of vaccines, the second generation of vaccines was developed by conjugating polysaccharide to a carrier protein.

This results in a boostable response and also protection in infants and children. These vaccines are still being produced, and there are still second-generation vaccines being developed. These are very complex products and propose challenges for regulation and for manufacturing. Taking advantage of newer developments in metabolic engineering and advances in glycoconjugate science, third-generation vaccines are being developed and are being presented to the agency that are based on metabolic engineering of bacteria to produce vaccines in various forms.

This third-generation vaccine itself is involving in newer techniques for glycoengineering. A fourth generation of vaccines that are coming along is based on things that we've learned over the years about

glycoconjugate vaccines and the structure of carbohydrates, where synthetic carbohydrates are based on both knowledge and rational design are used to make glycoconjugate vaccines. To that end, the Laboratory of Bacterial Polysaccharides has expanded to another research group that we deemed synthetic biology.

We have hired a new recruit to head that as a principle investigator for that group. That principle investigator is Dr. Maria Florencia Haurat who is in charge of the synthetic biology research group, and she's studying metabolic engineering of glycoconjugates. That's a part of CBER's initiative for advanced manufacturing. As with most of the scientific community, the SARS-CoV-2 pandemic resulted in decreased research activities across the FDA. In March of 2020, all non-COVID related research projects in CBER were halted.

There were, however, two SARS-CoV-2 related projects that were allowed to operate at approximately 25 percent work capacity during this period. The work capacity is based on allowed building occupancy. Those

were projects thar were headed by Dr. Akkoyunlo, who I believe was studying projects related to the cytokine storm caused by CoV-2, and Dr. John Cipollo, who's looking at the glycosylation of spike protein. In September of 2020, based on CBER policy, some of the laboratory staff of LBP resumed non-COVID related projects, working for about 8 to 16 hours per week on a voluntary basis.

Subsequent to that, that has actually been increased. Now I think we're up to allowed 30 hours per week, yet it's still on a voluntary basis. I wish to thank the site visit committee for their constructive input into evaluating our research program. Thank you for your attention. Any questions?

DR. HANA EL SAHLY: Thank you, Dr. Vann, for the overview. I see Dr. Portnoy. Dr. Portnoy, please turn on your microphone and camera.

DR. JAY PORTNOY: Hello. Thank you for the presentation. I think you work is doing is great, and I really appreciate the report that you did. Something you said during your report stimulated a question in my

mind, and that was the glycosylation of the spike protein for the Coronavirus that we're fighting right now. Has your group developed any evidence that the glycosylation would make a difference in terms of vaccine production because we know that messenger RNA produced by protein is non-glycosylated? Would glycosylation possibly change the effectiveness of a vaccine?

DR. WILLIE VANN: We don't know for the spike protein particularly. I think taking advantage of the work that Dr. Cipollo has done with influenza, he does know with flu that glycosylation actually does affect function and glycosylation can affect the interaction of that vaccine with the immune system and also can affect production because with flu, for example, he can produce that in various substrates. Changing substrates can actually affect glycosylation. We're gathering information that could be useful. We don't know for sure yet.

DR. JAY PORTNOY: It sounds like an important avenue of research to pursue. Thank you very much.

DR. HANA EL SAHLY: Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you so much for that presentation, Dr. Vann. I had a couple of questions that are mostly structural and visionary. One of them relates to recruitment and detention of diverse workforce. I just had a couple of questions about how your lab and your whole system works towards that, and particularly for promotion of those individuals within your laboratory system. My second question relates to any collaborations between the laboratories that you have -- there was some mention in the first slide -- and partnerships with academia and other external and how that might actually allow you to progress at a more rapid (audio skip).

DR. WILLIE VANN: I'll briefly answer your last question first in that there are extensive collaborations with academia and not just in this country, around the world. Yes, there's lot of collaboration with the scientific community in these fields. You wanted to know about career development, I presume. Right? One of the things that actually

happened at this site visit is we had four scientists who actually were up for review, who were actually up for a promotion or who actually we had promoted.

We asked the site visit committee to evaluate their research progress. What we do is we have staff scientists that actually are researcher-reviewers. They have a role in review of products. They're a part of chemistry and manufacturing review teams and also clinical assay review teams. They are very active. A very important part of their research, in fact more than half of it, is actually original research. We evaluate them based on, one, how they perform in review, and we evaluate them based on how their research program goes, how they perform, their creativity, and productivity. Is that addressing your question or do you have further questions?

DR. HAYLEY GANS: Thank you. Thank you for that clarification. I was curious about mitigation of biases. I understand that there is only four people at (audio skip) limits the amount of (audio skip).

DR. WILLIE VANN: To address the diversity

issue, at least in my lab, we have a fairly diverse lab, to be honest with you. There are all sorts of people but people from various backgrounds, quite different backgrounds, including people who are immigrated from other countries, African Americans, Hispanic people. My lab isn't that big, but it's actually quite diverse. When I go out looking for people, I look for who actually can best do the job. That's probably the only way to do it, but I try to include people if I can.

DR. HANA EL SAHLY: Dr. Vann, quick question. You mentioned that the lab is still not functioning at full capacity. Did I catch that correctly?

DR. WILLIE VANN: That is correct.

DR. HANA EL SAHLY: Are there plans in the near future for expanding to full time?

DR. WILLIE VANN: That's above my pay grade as to when that's going to happen.

DR. HANA EL SAHLY: Any other questions for Dr. Vann? I see no raised hands. Thank you so much, Dr. Vann, for the presentation and for all the work

you've been doing. Next, we will take a 10-minute break. It's 8:35, so we will reconvene at 8:45.

[BREAK]

MR. MICHAEL KAWCYNSKI: Welcome back from that little break to the 168th meeting of the Vaccines and Related Biological Products Advisory Committee. Dr. El Sahly, are you ready to take it away?

OPEN PUBLIC HEARING - NO REGISTERED SPEAKERS

DR. HANA EL SAHLY: Thank you, Michael. The next session is designated for the open public hearing. However, no formal oral requests were received, and we will be now moving to the closed session. Michael, let us know when we are in the closed session, please.

MR. MICHAEL KAWCYNSKI: Let me make an announcement here. We are going to be moving to the closed session. This session will take us all the way through up to our lunch time. We will reconvene to the

public session immediately following. For the viewers, to keep you entertained, we will be putting up some music just so that you're entertained during this timeframe. Keep in mind we'll probably be coming back -- Kathleen, can you confirm with me -- roughly around 12:15. Does that sound about correct?

MS. KATHLEEN HAYES: That may be a bit early since we're running ahead of schedule. It'll be following a lunch.

MR. MICHAEL KAWCYNSKI: Again, at this time, we will be moving to the closed session. At this time, I will be moving you in a second here. I'm going to send you off over the closed session now. To the public, like I said, we are going to play some music for you and at least give you something to be entertained during this timeframe. For that, thank you, and we will see you and reconvene right after lunch.

BREAK FOR CLOSED SESSION

TOPIC II: STRAIN SELECTION FOR THE INFLUENZA VIRUS VACCINES FOR THE 2022 SOUTHERN HEMISPHERE INFLUENZA SEASON

MR. MICHAEL KACZYNSKI: All right. Good afternoon. We're getting close to afternoon. Welcome back. I know we had that long pause for our closed session and lunch. So let's get started. Welcome back to the 168th meeting of the Vaccines Related Biological Products advisory committee meeting. I am going to hand this back to Dr. El Sahly. Are you ready to take it away? Let's make sure you're not muted. Hold on one second. There you go. Now you're unmuted.

DR. HANA EL SAHLY: Good afternoon, everyone, and thank you for coming -- attending the (audio skip) today during which we will be reviewing the data that led to the selection of the influenza virus strain for the southern hemisphere 2020-2021. We will begin the meeting with Kathleen Hayes who will be going over the conflict of interest statement. Kathleen.

CONFLICT OF INTEREST STATEMENT

MS. HAYES: Great. Thank you, Dr. El Sahly. Okay. I'm going to read the second conflict of interest statement for today's meeting. The Food and Drug Administration is convening virtually today, September 30, 2021, for 168th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. This afternoon, for topic two, the VRBPAC committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccine for the 2022 southern hemisphere influenza season.

This topic has been determined to be a particular matter involving specific parties. With the exception of the industry representative member, all standing and temporary voting or temporary non-voting members of our PAC are appointed special government employees or regular government employees from other agencies and are subject to federal conflict of

interest laws and regulations. Based on today's agenda, all financial interests reported by committee members and consultants, no conflict of interest waivers have been issued under 18 U.S. Code 208 in connection with this meeting.

Dr. Jay Portnoy is serving as a temporary consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee and hence do have voting privileges and they do participate in the closed sessions as held. Dr. Paula Annunziato of Merck is currently serving as the industry representative to this committee.

Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. However, industry representatives are not appointed as special government employees and serve as non-voting members of the committee. They are not authorized to attend any closed sessions as held. We have the following consultant serving as the

temporary non-voting member and speaker for this meeting, Dr. David Wentworth.

Dr. David Wentworth is employed by the Centers for Disease Control and Prevention as Chief of the Virology Surveillance and Diagnosis Branch in the Influenza Division. He's an internationally known expert in influenza virus epidemiology, worldwide influenza disease burden, and influenza virus vaccines. Dr. Wentworth is a regular government employee and has been screened for conflict of interest and cleared to participate as both a speaker and as a temporary non-voting member for today's meeting.

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

FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and, if known, it's direct competitors. We would like to remind members, consultants, and participants that if the discussions involve any other product or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement and their exclusion will be noted for the record.

This concludes my reading of the conflict of interest statement for the public record. And I would like to hand the meeting back over to Dr. El Sahly. Thank you.

DR. HANA EL SAHLY: Thank you, Kathleen. Happy to introduce now Ms. Anissa Cheung who is the Regulatory Coordinator at the Division of Viral Products. She will do the introduction to the meeting and the presentation. Ms. Cheung.

INTRODUCTION AND PRESENTATION OF QUESTIONS

MS. ANISSA CHEUNG: Thank you. Can you hear me?

DR. HANA EL SAHLY: We can.

MS. ANISSA CHEUNG: Okay, thank you. My name is Anissa Chueng and I am working for the Division of Viral Products as a regulatory coordinator. And I'm going to introduce the topic for today's VRBPAC meeting. The purpose of today's VRBPAC discussions is to make recommendations for the strain of influenza A H1N1 and H3N2 and B viruses to be included in the 2022 southern hemisphere formulations of influenza vaccines licensed in the U.S.

Since 2016, U.S. vaccines manufacture has been approved to produce southern hemisphere formulations of the egg-based influenza vaccine. Vaccine strain recommendations and subsequent approval for southern hemisphere formulations follow the same process as the northern hemisphere. After my introduction, you will

hear the presentation from our CDC colleague, Dr. Wentworth, to present the epidemiology data of the circulating strain. You will hear the surveillance data from the U.S. and around the world summarized from the most recent WHO southern hemisphere strain selection consultation.

You will also hear the antigenic relationships among the contemporary viruses and the candidate vaccine strain. Among the method and techniques that you will be hearing about include the hemagglutination inhibitions and virus neutralization test using post-infection ferret sera and panels of sera from humans receiving recent inactivated influenza vaccines. Also some data on the antigenic cartography as well as phylogenetic analysis of HA and NA genes for all these recent circulating strains and candidate vaccine strain.

Oh, sorry, I have to -- to quickly review the previous recommendation for the 2021 influenza vaccines. For the southern hemisphere influenza vaccines, last year on September 25th WHO recommended

the following strain: for the egg-based trivalent influenza vaccines in the 2021 influenza season, southern hemisphere, winter, an A/Victoria/2570/2019 (H1N1)pdm09-like virus, an A/Hong Kong/2671/2019 (H3N2)-like virus, a B/Washington/02/2019-like virus which is from the B/Victoria lineage.

For the quadrivalent vaccines containing two influenza B viruses the WHO recommended the above three viruses and a B/Phuket/3073/2013-like virus which is from the B/Yamagata lineage. On October 2nd, 2020 VRBPAC met and recommended the same strain as the WHO for U.S. manufacture of the southern hemisphere formulation. For the northern hemisphere influenza vaccines earlier this year on February 26th WHO recommended the following strain: for the egg-based trivalent influenza vaccines in the 2021-2022 influenza season for the northern hemisphere, winter, an A/Victoria/2570/2019 (h1N1)pdm09-like virus, an A/Cambodia/e0826360/2020 (H3N2)-like virus, and a B/Washington/02/2019-like virus which is from B/Victoria lineage.

For the quadrivalent vaccines containing two influenza B viruses the WHO recommended the above three viruses and a B/Phuket/3073/2013-like virus which is from the B/Yamagata lineage. A week later, on March 5th, VRBPAC met and recommended the same strain as WHO for U.S. manufacture of northern hemisphere formulation. So to summarize where we are at this point, the WHO met last week and made recommendation for strain that should be included in the southern hemisphere 2022 influenza vaccines.

The WHO recommended the following strain for the egg-based trivalent vaccines for use in the 2022 southern hemisphere: an A/Victoria/2570/2019 (H1N1)pdm09-like virus, an A/Darwin/9/2021 (H3N2)-like virus, a B/Austria/1359417/2021-like virus which is from a B/Victoria lineage. For the quadrivalent vaccines containing two influenza B viruses the WHO recommended the above three viruses and a B/Phuket/3073/2013-like virus which is from a B/Yamagata lineage.

The H3N2 and the B/Victoria lineage strains

are the two new strains recommended by the WHO for the 2022 southern hemisphere influenza vaccines. So very soon you are going to hear the presentation from Dr. Wentworth. And after his talk the committee will discuss which influenza strain should be recommended for the antigenic composition of the 2022 southern hemisphere formulation of influenza virus vaccine produced by the licensed U.S. vaccines manufacturer.

And at the end of the discussion the committee will be asked to vote for the following questions: first, for the composition of egg-based trivalent 2022 southern hemisphere formulations of influenza vaccine does the committee recommend inclusion of an A/Victoria/2570/2019 (H1N1)pdm09-like virus, inclusion of an A/Darwin/9/2021 (H3N2)-like virus, inclusion of B/Austria/1359417/2021-like virus from the B/Victoria lineage? Second, for quadrivalent 2022 southern hemisphere formulations of influenza vaccines does the committee recommend inclusion of a B/Phuket/3073/2013-like virus, a B/Yamagata lineage as the second influenzas B strain in the vaccine?

I believe this is my last slide and thank you for your attention.

DR. HANA EL SAHLY: Thank you, Ms. Cheung. Do we have any questions for Ms. Cheung before we move to (audio skip). I do not see any raised hands.

It is my pleasure now to introduce Dr. David Wentworth who is the Chief of Virology Surveillance and Diagnosis Branch Influenza Division at the National Center for Immunization and Respiratory Diseases at the CDC. Dr. Wentworth is going to go over the data that led to the strains recommended by WHO. Dr. Wentworth.

WORLD SURVEILLANCE

DR. DAVID WENTWORTH: Hello, thank you. Can you hear me okay?

DR. HANA EL SAHLY: We can.

MR. MICHAEL KACZYNSKI: Yes, we can.

DR. DAVID WENTWORTH: Okay, great. All right, thanks very much. I'm gonna turn my video off just so that --

MR. MICHAEL KACZYNSKI: You're good, Dr. Wentworth. You're good. You're good. All right.

DR. DAVID WENTWORTH: Okay, thank you. So we'll get started here. Do I have control of the slides, Mike?

MR. MICHAEL KACZYNSKI: Give me one second. There, take it away.

DR. DAVID WENTWORTH: Thank you --

MR. MICHAEL KACZYNSKI: There you go.

DR. DAVID WENTWORTH: -- very much. Excellent. So here is the outline of what we will be talking about today. I'll provide an overview of the recommendations and then we'll go into some of the influenza activity that we saw, which was very low due to the Covid pandemic. Then I'll describe the (H1N1)pdm09 viruses, and I'll be focusing on the major highlights there. This is in part because the recommendation is the same as the northern hemisphere 2021 and 2022 season, and the southern hemisphere 2021 recommendation.

I'll also be talking about H3N2 viruses. I'll

spend more time on this one, provide details central to the recommendation, which is an update from the previous 2021 southern hemisphere recommendation. And I'll be describing some of the similarities and differences between the northern hemisphere 2021-2022 recommendations which we're getting this fall. And some may have already gone out and received it, so good job doing that. The B/Victoria lineage, we'll be providing details central to the recommendation there as well.

It was an update from the previous southern hemisphere 2021 recommendation. And for the B/Yamagata I will not cover the recommendation remains the same and there is no circulation of lineage -- this lineage during this period. Okay. So the WHO consultation meeting really depends on year-round surveillance conducted by the Global Influenza Surveillance and Response system, also known as GISRS. Within this system there are WHO collaborating centers such as your CDC, National Influenza Centers, WHO Essential Regulatory Laboratories or ERLs, and WHO H5 reference

laboratories.

And it's supported also by many countries and partners including the GISAID which is the Global Influenza Sequence Database structure. And it's been heavily used for SARS sequence information as well. So the WHO consultation meeting was held from September 13 through 24th, 2021. It was a virtual meeting. It was chaired by Kanta Subbarao, who's pictured there to the right, and 10 advisors were participating in the meeting. Eight of the advisors are focused on the seasonal influenza and represent their corresponding WHO Collaborating Center or Essential Regulatory Laboratory. They're pictured below.

And then there were 42 observers from WHO CCs, ERLs, academia, H5 Reference Laboratories, as well as the veterinary sector. Actually, this week is ongoing the Zoonotic vaccine consultation meeting where our pre-pandemic viruses are selected. And that's happening right now and that's part of -- the old flu is part of that as well. And then we have experts from WHO regional offices, et cetera. So here were the

recommendations and I already alluded to this in the outline.

For the quadrivalent egg-based vaccines the H1 stayed the same, A/Victoria/2570 from 2019, the H3, they're highlighted in blue. Those that changed is updated to -- for the southern hemisphere to recommend an A/Darwin/9/2021 (H3N2) virus and the B/Victoria lineage was updated to a B/Austria/1359417/2021 virus. And the B/Phuket stayed the same, 3073. And the green boxes indicate what would be used in the trivalent vaccine. And then for cell and recombinant-based vaccines, again, the H1 recommendation remain the same as an A/Wisconsin/588.

The cell for H3 was recommended the Darwin/6, closely related to the Darwin/9/2021 and a cell isolate of the B/Austria/1359417. So there was both an -- we call that an egg cell pair. So the same swab an isolate was obtained in an egg, and an isolate was obtained from cell culture. And then B/Phuket was recommended. Okay. This slide illustrates the number of specimens processed by GISRS at a weekly level. I

think people don't appreciate how much -- how big this GISRS network is. And we're typically -- and this is over a number of years. The key is down here, 2018-2021.

So the number of put specimens tested can be, you know, range from the peaks of more than 150,000 weekly down to about 40,000 weekly down in these weeks, you know, 24 through 25, 26, those kinds of timeframes. And many people think because of the Covid-19 pandemic there wasn't testing but you can actually see the past two years in the yellow 2020 and the red 2021, there has been more testing than average. But despite a lot of that testing the percent positivity's been quite low.

Usually this Y-axis here is in the thousands, not the hundreds. But you can see on a weekly basis we are still getting the viruses that are testing positive over the course of the year. And then the color coding in these bar charts show the blues are the A(H1) and the H3, so that the influenza A viruses are all the different color blues. The lightest blue being -- I

hope you can all still hear me. My computer was doing something funny. The lightest blue being the H1N1, the aqua being H3, and the dark being not subtyped. And then the B/Victoria lineages are the orange. Or, I mean, the B lineages are the orange, the Victoria being dark, Yamagata being very light. And you can see very few Yamagata lineage viruses there, for example, that were detected.

All right. And then for the southern hemisphere we had a very similar kind of range of viruses but even lower detections as you can see on the Y-axis. Now looking at the percentage of positive influenza A and B viruses from February to August 2021 you can see that the type A viruses represented 40% of this pie chart here, that you can see over here. And the type (H1N1)pdm09 represent 20%, and the H3 dominated with 80%. But the type B viruses, they represented more than the type A at 60%. And B/Victoria far, far greater than B/Yamagata.

And so you can see that B/Yamagata, this little slice of the pie here, where it was detected.

All right. Moving on to the influenza activity globally. Here you can see, again, the H1's and H3's are in the blue colors and the influenza A and the B are in the orange colors. And so you can see -- this just gives you a sense of the distribution of influenza virus by type and subtype globally. You can see, for example, that in China there was an awful lot of influenza B and little influenza A.

In the U.S. we're more of a half and half portions during this time period. And in parts of Africa like western Africa there was more H1 than H3 and more A than B but in South Africa it was different. And so that gives you a good sense of the geographic distribution of the activity. Now this slide illustrates the genetic characterization of influenza viruses by the WHO-CCs going from the period February to August 2020 and February to August 2021.

And so you can see there was just more viruses circulating in the 2020 timeframe than there has been in the 2021 period. But there were still a number of viruses characterized across all these different

subtypes and lineages. Again, with the Yamagata being no viruses in this timeframe for characterization. Okay, so now we're getting into the H1N1 viruses. Here you can see the number of H1N1 viruses detected by the GISRS in the past couple of seasons. Again, 2020 is yellow and 2021 is this orange/red color.

And you can compare that to the 2019 season where you see the large peak of viruses detected. But here you can see this fall during the spring of 2020 as the Covid-19 pandemic really took hold. And then it flatlined across there as far as the circulation of H1N1. So there's been a very low level circulation of H1N1, even lower than B or H3N2 viruses. This slide illustrates the activity as a percent positive globally. And so you can see the different countries where activity was detected at zero to 20% level. Quite a few countries globally and continents globally had that.

And you can also see in parts of western Africa very high positivity's, you know, 40% to 80% positivity rates there and in parts of Europe, et

cetera. Now this slide I'll take a little bit of time on because it is very full of information. But the main points are listed in the bullets. And so with the H1 HA phylogenetic tree, which is shown on the right-hand side here, starting with some of the older viruses down here in the older clades -- 731, blah, blah, all these coming up the tree. Until we get into clade five, which is the dominate clade right now, 5A being the most common.

And so that's kind of moving the evolution this way from the past. But you can also see where it bifurcates or splits into two different groups. And so we have the 5A1 viruses which are colored in this salmon color here, the 6B1.5A1 viruses. And they really split right about here at this D187, 189 position. So there's a D187A, Q189E substitution that's generally a hallmark. And there's a genetic split, but it encodes that substitution.

And then many of these viruses have been circulating. You can see over here, these are the months of the year. This is basically 2021 in the

middle to the right-hand side of all these lines. And these orange dashes mean these were from Africa. And then you can see specifically those from western Africa like Togo, for example, which is this virus here. And so these 5A1 viruses, as I mentioned, share these 187. It also is the 2020 - '21 vaccine prototype antigen.

And that's illustrated by that arrow here, this Hawaii/70 virus that now they use in assays that I'll show you later. And I mentioned the recent viruses from South Africa. I didn't mention we see very few viruses with this unique substitution, G155E. But that, we know, is an important site and so we've included it. That's like this one here, this North Carolina/04 or 01/2021. And we've included it in some assays but I'll show you that. Now getting into the 5A2 viruses.

This is this area shaded in blue. It encompasses this Wisconsin/588 northern hemisphere '21-'22 cell prototype. So that's this season. So this is the prototype of the vaccine virus we'll be getting this fall and it's also the southern hemisphere 2022

recommendation. Okay. These often share this substitution here N156K. Again, a very important antigenic region of the virus. So we keyed in on that pretty early on in the emergence of this group of viruses.

I mentioned the vaccine recommendations and it includes recent viruses from India which you can see here, you know, this is May, June, July, into August. You know, August is getting to a point where you don't see very many viruses for this type of selection because they have to be identified and sequenced, et cetera. So right up to the minute is what I'm trying to say there. Now, getting into a very simple way of looking at antigenic data. This is called antigenic cartography.

We've talked about this before. But it's a way to take data from tables and put it graphically onto a map. And what you can see are these viruses with the HA from the 6B.1A subclades 5A1, those 187 viruses, they're down here, and the 5A2 viruses, they're up here, form two antigenically distinct

groups. They're easy to see on this chart or graphic scale. The viruses of each subclade cluster together, as you can see here. And you can see here, there was a whole bunch of 5A2 viruses circulating prior to September 2020.

And they're -- the older viruses are indicated in gray in this document, on this picture. And then we have the 5A viruses that have the G155E. These are shown in this yellow color. So they're forming a slightly different group. Again, they're in this 5A group but they're a slight different emergence from the 5A1's, like the Hawaii/70 prototype. Okay. Now this slide illustrates human post-vaccination sera analysis of the (H1)pdm09 viruses. And this is now showing you data from sera collected from recipients of the northern hemisphere 2020 - '21 vaccine.

So last year's vaccine sera was collected about December or so from people that had been vaccinated and then used for this analysis. And so, we have sera panels from pediatric populations from six to 35 months, all the way through over 65-years-old from a

variety of vaccine platforms, egg-based, cell-based platforms, and also high dose vaccine here in the elderly. And the easy takeaway from this is blue is good.

And the orange colors represent statistically significant reductions in neutralization by that antisera against various viruses tested, which are at the top of these columns. And so, the 5A1 viruses are this whole group of viruses here until we get to the blue box. And then the 5A2 viruses are these blue boxed viruses. And so what you can see for the most part is the 5A1 viruses are pretty well neutralized by sera from these vaccines which was a 5A1 vaccine. And the 5A2 viruses -- sorry, the 5A2 viruses are not neutralized so well or escape.

And that's shown -- that's -- basically the take home is in this bullet here. The GMT to the 5A2 viruses were low in all the serum panels. We can see that as you track your eye down. This is data from CDC as well CBER, NIBSC. So multiple Collaborating Centers or Essential Regulatory Laboratory's finding the same

type of data. Okay. So now, this is a good piece of interesting information. The southern hemisphere 2021 vaccine was a 5A2 vaccine, so it was a Wisconsin/588-like vaccine.

And so now we can take sera from Australia, from adult and elderly population. And we can see how well it works against the 5A2 viruses which were poorly covered using the vaccine before. And how it cross protects against these 5A1 viruses very well. Most of the viruses tested, some of these that I showed you on the tree that had unique substitutions, such as these new emerging 166/186 substitutions with Togo/881 virus or the G155E. So that was the only virus that really showed low reactivity with this new sera. And so that's the take home message here.

Post-vaccination sera from the southern hemisphere, which is a 5A2 virus, inhibits both 5A2 and most 5A1 viruses. With the exception being that odd G155E viruses which are relatively rare. But we keep our eye on them now. Okay. So here's the H1N1 summary. There was low circulation, but (H1N1)pdm09

viruses were detected in West Africa, India, and sporadically in a few other regions. The great majority of the HA gene sequences belong to the 5A subclades with 5A1 HA proteins predominant in West Africa.

They had a few additional substitutions which we tested in the human serology and ferret serology data. And the 5A2 virus HA proteins were seen in recent viruses from India. And those I pointed out on the time tree where some of the most recent viruses circulating are these. They have a few additional substitutions, which I won't read out. But just for context there you can see they're still evolving. And characterization with the ferret antisera showed that the 5A1 and 5A2 viruses are antigenically distinct from each other.

And antisera to 5A1 viruses well recognized 5A1 viruses but not 5A2 and vica vera with the Wisconsin/588 sera. And that's evidence for them being antigenically distinct from each other. Now given that antigenic distinction, we found that post-vaccination

sera collected from humans vaccinated with the northern hemisphere reacted well with the 5A1 viruses but not those 5A2 viruses. Whereas, those given the southern hemisphere 2021 vaccines with their 5A2 antigens had sera that inhibited both 5A2 viruses and well recognized viruses representing most of the 5A1 groups that are circulating.

As far as antiviral susceptibility, we always look at this. It's not really part of vaccine strain selection but it's a good time to understand whether there's resistance emerging out there. And the good news is we didn't find any resistance, really, in the H1N1 viruses. I won't read those to you, you can read that. Okay. Now we're going to turn our attention to the H3N2 viruses. And so, we can buckle up for this. The H3N2's are a quite dynamic set of viruses. Again, now looking -- focusing at the H3N2 viruses protected as part of the GISRS network.

Again, seeing lots of viruses circulating in previous seasons and very low circulation in the past couple of seasons. But you can see here in weeks 30

through 36, and probably this downturn is a reporting lag, some increase in the H3N2 viruses that are circulating. And where are those circulating? You can see on this map the percent positivity. Again, color coded in this key here. We saw quite a bit of circulation in Southeast Asia and in South Asia and India. Also in Nepal, in parts of Africa -- northern Africa and a little bit in Western Africa and some parts of Europe.

Okay. And so we had viruses in all these locations, including the Middle East, to look at. And this gives you a very 50,000-foot view of the phylogenetics of the hemagglutinin gene of the H3N2 viruses with quite a bit of time to look at them. And I put this in on purpose because I want to illustrate that many clades co-circulate. That's what you can see here. In 2019 we had 3a viruses and 2a viruses all co-circulating around the globe at that time. And that's dictated here.

And now we saw the emergence of many 2a1b subclades. That's highlighted in the salmon color with

the 2a1b, 1a, 1b, 2a, and 2b which I'll be walking through. And the 2a1b1a clades and 2a represent some of the most recent viruses circulating. You'll see that out here on these tiny little dashes that I'll drill into in more detail on this next slide. Okay. So this next slide, again, is a highly integrated tree with a lot of information on it. We're going to walk through it a little bit slowly.

The take homes here, nearly all the viruses now have this 2a1b HA gene which continues to diversify. And so the 2a1b now have this -- the 1b group of viruses represented by the Hong Kong/45. That's down here on the tree. This was the southern hemisphere 2021 vaccine prototype virus. It's hard to read probably but it's in the red there. And they had these common amino acid substitutions, this 135K and 137F that gave rise to this whole group of viruses that really dominated at one point.

They also -- this branch point also has the 1a viruses which are this bullet here, represented by this New York/21, for example, which is a serology antigen.

And they diversified further into something like this Togo/771 at the top of this little section of the tree and Niger/8749 right here. And then the most recent viruses are these 2a viruses represented by this boxed out salmon color here. That's where the 2021 - '22 northern hemisphere vaccine prototype is, the Cambodia virus.

It's the Cambodia/E0826360 from 2020 that you all recommended or included in the vaccine in the spring in March for us this fall. And then the 2022 southern hemisphere recommended prototype is up here for your consideration, the Darwin/6. And so the two -- these are closely related viruses, they're in this 2a group. A little bit further evolved to this group now is this 2a2 or are these 2a2 viruses represented by this Bangladesh/1006. That's basically at the base of this group of viruses in this tree.

So they often have this 159 change which is this bunch of changes here, 159 being a pretty important amino acid in antigenicity. So now this slide illustrates the final geography a little bit

easier than that detailed slide I just showed you in that HA tree. And what it's really showing you in this left-hand panel is the September 2020 to January 2021 versus the right-hand panel February 2021 to August 2021.

And what you can see is this transition of the subclades, the 2a1b subclades, the global distribution of the 1a and 1b, which are these yellow and aqua colored dots decreasing, and the distribution of the 2a viruses which are the more greens and the lighter kind of mustard color here, the 2a viruses increasing. And you can see that the 2a2, this forest green virus, increased and the 2a1 viruses continued to circulate. So we've got a decrease in the 1a1b and an increase in the 2a happening.

Now this gives you an impression of what all that genetic changes are doing to the protein. It's the major antigen in our vaccine, that's the hemagglutinin. On the left, southern hemisphere vaccine prototype, the Hong Kong/45 cell. And it's illustrating a variety of important regions of the HA

molecule. The receptor binding site is circled here. And so that's where the virus attaches, the actual part of the molecule attaches to the host cell. And you can see these major antigenic sites such as B and A right around that receptor binding pocket.

So our antibodies in these sites really block that ability of the virus to bind. And antigenic sites E and D also play a role as well as C. And so you can see they're all color coded here. Now when we look at our northern hemisphere 2021-2022 prototype, the Cambodia virus, I won't read that whole number to you again, you can see all these changes are highlighted in red around the molecule. You can see multiple changes in many important epitopes, primarily in antigenic site B and A here. And you can also have a look at this Darwin/6 which is the recommendation.

It shares many of these same changes but has this additional Y159N. You can now see where it is on the molecule right up near the top and very close to the receptor binding pocket. And the T160I which also is important because it removes the glycosylation motif

at position 158. So kind of important substitutions but just a few additional substitutions on top of what's there in the Cambodia virus. Now this slide is an overview of the neutralization data to antisera by the antisera to the antigens recommended for the '21 southern hemisphere vaccine virus. And so that was Hong Kong/45-like.

You can see multiple Collaborating Centers here. Again, low levels of viruses compared to normal but still representative of the viruses circulating in each of the catchment areas. And you can see that 92% would be considered low to that vaccine virus. So that's not a good situation with the cell-like candidate. And it gets worse when we take the egg antigen with 100% of those being considered low or eight-fold reduced or more. So moving now to the neutralization by Cambodia.

So this really isn't relevant to the southern hemisphere per se, but it could be a choice that the southern hemisphere could use similar to the northern hemisphere. And you can see definitely better coverage

than the Hong Kong/45 with 64% being considered like and only 36% being considered low. A little bit greater with the egg and that's always expected. The next slide. This is now showing you antigenic cartography from the two centers. All the centers participate in this but it's hard to show all that data.

Here we're showing data from our center in Atlanta as well as data from Melbourne on the right-hand side. So we use something called HINT which stands for High Content Imaging Neutralization Test to look at the viruses and how well the antisera to viruses neutralize them. And so we can see that these are forming different groups. So there's the Hong Kong/45 cell-like virus is this orange dot or kind of fuchsia dot and the Cambodia recommendation is this orange dot.

And you can see many of the viruses in this time period are clustering with this orange group of viruses and overlapping a bit with the Hong Kong/45 serum. And then we have this Bangladesh virus, this

2a2 group of viruses are colored in this kind of a mustard color, a brown color, and a lighter yellow color. We were interrogating whether this additional substitution at 156 mattered or not. And the data illustrates that it really doesn't matter. You're seeing viruses of all flavors, the dark, the light, and the medium orange colors all clustering very closely together with antisera to this Bangladesh/1006.

And then CC Melbourne has very similar data but they had a lot more of these viruses with the 156S circulating in their tested viruses. So you can see that here, this darker color. But you can also see where the Bangladesh/1006, which is very similar to the Darwin/6 that is recommended as well as Darwin/11 which is the qualified manufacturer cell candidate, and Darwin/9 which is the egg virus that was recommended. All very antigenically related to this group here and divergent distinct from Cambodia or Hong Kong.

All right. Now we'll look at the human serum post-vaccination analysis with the H3N2 viruses now relative to the cell propagated Hong Kong. And so you

need to set things at 100% to do the analysis. And then we are looking across -- and again, orange -- any orange color meaning significant reductions in neutralization. And the major clades of each of these viruses that are named at the top of the columns here are listed above just for simplicity. We have the 1b, the 1a, the 2a1, and the 2a2 viruses as well as 3a viruses.

And really what you can see is these 2a viruses, which I just boxed out with the pointer, really represented some of the viruses with the lowest reactivity to serum after vaccination with the previous vaccine candidate. And the take home is really here that multiple serum panels show these 2a viruses escape neutralization. And that these 2a2 viruses, like you can see here -- you can cast your eye down this Bangladesh column, and down the Wisconsin/02, and Delaware/01, as well as the Darwin/6.

All showing, you, Delaware/01 and Darwin/6 are basically the same hemagglutinin molecule but just from different isolates across the world. Anyway, the two

2a2 viruses are the lowest. And now we're looking at the antigenics. So now you can actually see some data. I won't show you all these tables, that's what the cartography is for, but it's nice to look at some specifics here.

So if we take ferret antiserums for the southern hemisphere 2021 recommended viruses, that's these two columns here, Darwin/726 would be equivalent of Hong Kong/45 and Hong Kong/2671 is the egg prototype. And so the red coloring here is greater than eight-fold reductions. And so you can see that a lot of the viruses tested, they did test antigens in this timeframe, are quite low to this. So they're poorly inhibiting the clade 2a1 and 2a2 viruses. They do a pretty good job on the other virus clades but not many of those represent recent test viruses.

The dates are over here of some of these isolates. And so when you take a look at the northern hemisphere reference virus, like the Cambodia virus -- here's a cell and egg, you can see pretty good reactivity, or at least modest reactivity with these

recent viruses. And good reactivity with the 1a viruses which are like themselves. And so from that you're seeing they inhibited the 1a, 1b, 2a1 viruses but show some reductions in the 2a2 viruses tested.

And then if you look at sera against the 2a2 reference virus, which is here, and the cell is this first column down here, Darwin/6. You can see how well the light-yellow color -- it's less than four-point reductions to the homologous titer of 640 here, how well all of these circulating viruses from Darwin, Nepal, Philippines, Victoria, were against that virus. Darwin/11 is the qualified manufacturing cell line isolate. So if you're using cell culture vaccines that would be the seed.

And then for egg-based vaccine, Darwin/9 is the seed prototype and that is also showing quite good reactivity for an egg isolate for those most recent viruses. Now this slide moves us now to the antigenic cartography showing you serum circles. So now, how well -- so everything within the circle is considered covered very well, four-fold or less by, say, for

example, serum against Darwin/6. It covers all these viruses and comes out to the 2a virus, 2a1-like viruses.

So we're covering these 2a2 but comes out to these 2a1's and starts covering those as well. And here's the Darwin egg, it's a little tighter serum circle. But again, really do a good job covering the diversity of that new group of viruses. So to summarize the H3N2. Hopefully, I have been clear about this. This is a complicated set of viruses usually and a lot of evolution there. We saw in many countries, areas, and territories that were reporting influenza A viruses that H3N2 subtypes were detected.

But some of the details are here. They are in countries in Southeast Asia, South Asia, Middle East, Africa, Oceania, North America, Europe. With regard to the biogenetics of the hemagglutinin gene for the circulating H3N2 virus over this period, all really belong to this 2a1b subclade. And that nomenclature is getting quite long and I understand that. That's why I short-handed it often when I'm discussing it to the 1a

group which have those amino acids, the 1b group, and I folded here the 2a which represent most of the viruses now that are kind of taking over.

And they have split into this 2a1 group and the 2a2 group. But they are quite genetically related viruses. And so the viruses in the 2a2 represent an increase in proportion. We showed you that in some of the maps where we're now pushing towards the 2a2 dominating over 2a1, which dominate over 1a and 1b. But as with always H3N2 viruses there's co-circulation of these different groups both in different geographic regions and simultaneously in various regions. To summarize the antigenic characteristics.

The 2a2 viruses are antigenically distinct. And that's really illustrated by this data here. Ferret antisera to Hong Kong neutralizes the 1a1b virus as well. And 2a1 virus is a cross-protection against those pretty well. So it was a good vaccine choice. But it neutralizes the 2a2 viruses poorly. The Cambodia virus for the northern hemisphere 2021-2022 season reacts well with 1a, so it's kind of back

protecting against some of the older viruses, the 1b and of course the 2a1 viruses which is its subclade.

But the 2a2 viruses, we're showing some reductions there, that sera. And then the Darwin/6 recommendation for the '20-'22 season in the southern hemisphere well recognizes the 2a2 viruses but doesn't do a very good job against the 2a1 viruses. So it's a little bit more reduced than the other way around and it poorly reacts with 1a and 1b viruses. Now to summarize the serology.

We've found that the studies with the serum panels that vaccinated against the Hong Kong/2671-like or Hong Kong/45-like viruses which are in that 1b clade, the GMT's, the Geometric Mean Titers were significantly reduced against the cell culture propagated 2a1's. That was kind of a burnt orange color. And then the darker orange color were those 2a2 viruses. And for the antiviral susceptibility, again, the good news is we're in good shape.

Of the viruses that were tested, collected after January 2021, none showed reduced inhibition to

neuraminidase inhibitors and all were expected to be susceptible to baloxavir. Now I'm going to change our attention to the influenza B viruses. And this slide is a familiar slide now. It kind of looks the same for all the viruses, this VRBPAC meeting, which it typically doesn't. But again, decreasing in the spring of 2020. And then continuing to be very low circulation in most parts of the world in 2021.

However, there were some countries in the world that had high circulation including -- and that will be shown here. China, for example, had very high levels of influenza B viruses circulating, as well as parts of Africa and Europe and even in some of the Americas. We had pretty good circulation. And so we had representative viruses to analyze from those epidemics and outbreaks. This is illustrating the phylogenetic tree of the B/Victoria viruses. Again, this is a high-level tree.

You can see from 2017 through 2021 here, you're not expected to see the details. But we had a number of clades that have co-circulated over those

years. And you can again see how global the circulation is. And we had this clade 1A.3, which is this big black bar here, which really dominated prior to the Covid pandemic. Which you can see all back here. And then the pandemic having happened really in the beginning of the spring of 2020 dramatic decreases in the viruses around.

And then what reemerged after that bottleneck, that Covid bottleneck, are these clade 1A.3a viruses which I highlighted in the blue color here. And you can see those, a lot of them, in China, for example. And they diversified into two groups. And we're going to look closely at that on the next slide. Here you can see this clad 1A.3. It's all the viruses really in this tree that predominated prior to the Covid pandemic. The southern hemisphere 2021 vaccine virus is shown down here, B/Washington/02/2019 on this tree, so it's this V1A.3.

And you can see all this evolution happening right at -- throughout all these viruses here. And part of this clade 1A.3 (N150K) substitutions. That's

this group of substitutions here. So they represented a very minor group of viruses prior to Covid-19 and expanded after Covid-19. And really represent most of the recent viruses. And they've split into these two groups, the 3a1 which are highlighted in this blue box at the top. And you can see when they circulated, all the dashes here, and where they circulated.

So this is red, this is in China. And then 3a2 viruses which are represented by this more salmon colored box down here. And that's where the southern hemisphere recommendation sits, the B/Austria/1359417 group. This has increased steadily in recent months. And you can see that in this time series slices here. And it's more globally disbursed. You see how there's multiple colors here. In Europe in green; North America, blue; Western Africa in orange; and China in red. So it's also in China.

And it's displacing the 3a1 group in China. So you can see here the 3a1 group dominating originally and now the 3a2 group displacing it and these guys diminishing. So that's kind of an interesting

phenomenon happening in China. Probably a microcosm of what we'll all see. Some of the viruses like this, so the B/Austria I already pointed out, and the B/Michigan/01, very similar to this B/Austria virus that's listed here. That will be in some of the serological assays I'll show you.

So this reiterates what I just told you. That globally we're seeing a lot of these 3a viruses. The 3a1's being a darker color, it's a little bit hard to see in China. But still over the whole time period representing a majority. And the 3a2 viruses in this lighter blue color such as that. And so you can just how those are more distributed than the 3a1 viruses even with our travel restrictions. So now we can look at the neutralization of the B/Victoria viruses by antisera recommended for the -- against viruses recommended for the 2021 southern hemisphere.

And that was the B/Washington/02 cell virus. And you can see a little bit of difference by the different centers, for example. The U.S., the CDC had about 60/40 split with being -- 60% being like.

Although very low numbers but still quite real. And then CNIC having very high numbers. This is the China National Influenza Center having very high numbers of viruses to test but really driving a percentage that are considered low. The Francis Crick Institute.

So overall we had 18 percent that were considered like and 82 percent considered low. That's suggesting we need to update the vaccine. A very similar phenomenon, and actually a slight improvement with the egg antigen. And this actually has a molecular reason. And that's because the egg virus has lost a glycosylation site that is naturally missing in the new emerging clade. So there's actually a little better cross-reactivity in this instance. Now this gives you a picture of cartography looking at the different viruses.

So you can see the B/Washington sera pointed in this black box here. The different virus types that were circulating and focusing on these bottom viruses here, the two green ones, the 3a1 and 3a2, those represent the most recent viruses. The 3a1's having a

little bit more cross-reactivity to that Washington sera. And the 3a2's, the lighter colored, being a little bit outside of that four-fold reduction in the serum circle. Here is the Washington egg, similar phenomenon.

And then here is the new recommended candidate which does a really nice job against this new emerging group but doesn't cross-protect well against the 3a1 viruses, the darker green viruses or the predecessor viruses like Washington/02. It appears that virus doesn't have as much breadth, really, as the Washington/02 virus did. But it does represent the antigenically distinct clade that's emerging. Now human sera, it always looks better because we have great cross-reactivity against influenza B viruses in humans generally.

And so what you can see here is these are now looking at titers relative to the vaccine antigens, cell Washington, the Washington cell virus here. And you can see nice reactivity with the 3a viruses. So these have that 150K change but don't have additional

substitutions like the 3a1 viruses which have that additional 220M that's listed on the tree. I didn't walk you through all these minor changes. But that was some of the major substitutions in that virus. And you can see that gives us some reductions in the human sera.

And the 3a2 viruses in two different flavors. This is this Michigan/01 and a Maryland/01. So this is a lot like the Delaware/6 that's named. They have the 127T, 144L substitutions. Probably likely very important. You can see some reductions in some serum panels but not huge reductions. Pretty good cross-reactivity with the Washington egg antigen. But still an indication that there are reductions in some of the human serum. And the take home from this -- I started to put these bullets in just to help because the human serology is a lot to walk through.

The geometric mean titers and the sum of the serum panels were reduced to the 3a1 and 3a2 viruses. Now looking at some of the reference viruses and potential candidate vaccine viruses that there are to

choose from. The recommendation in the southern hemisphere was this Washington/02. Some of the recent viruses isolated serving here as test antigens. The homologous titer of 160. So you can see this 3a1 covering pretty well, only a two-fold reduction. That's highlighted in the blue color, the 3a1 clade.

Whereas the 3a2 clade there were viruses from Cote d'Ivoire, Singapore, Gansu, you know, these are parts of China. There are more, Singapore and Philippines. So you can see how disseminated they are getting lower against that group. Serum against one of our candidates, that would be a 3a1 viruses, doesn't react very with this 3a2 viruses but reacts very well with itself, with its own group. And then the 3a2 group of viruses having a titer of 1280 reacting very well with all the 3a2 testing antigens.

Even though they have additional mutations, et cetera from that B/Austria virus. But not so well against the 3a1 group of viruses. For the B/Yamagata, I mentioned this earlier but just for posterity I have included this slide. We had sporadic detections of the

virus in 2021 but none were confirmed by Collaborating Centers and no viruses with collection made after March 2020 were available for characterization. So I won't show you any data on that. And then to summarize influenza B viruses.

The B/Vic lineage viruses predominated by a huge margin and no Yamagata lineage viruses were available for analysis, as I just told you. The HA phylogenetics of the B/Victoria lineage show that all the HA belonged to 1a3 now. These have a characteristic deletion and substitution in the HA1. There are subgroups of the 1A.3a viruses with HA genes that have additional substitutions such as that N150K substitution have emerged and split into 3a1 and 3a2 groups which are antigenically distinguishable.

The 3a1 having V substitutions like V220M seen almost exclusively in China. And the 3a2 with these substitutions listed seen in Asia, Africa, Oceania, Europe and North America as well as parts of Asia, including China. The number and proportion of the 3a2 viruses have been increasing steadily in the recent

months and they are geographically disbursed as you can just see from that point above. The second part of our summary for B viruses shows that the antigenic characteristics using ferret antisera, the subgroup 3a1 and 3a2 viruses are drifted from the B/Washington/02 viruses.

And the 3a1 and 3a2 viruses are antigenically distinguishable from each other. You can kind of remember those cartography maps that I showed with the different colored green dots fostering in different spots. The antisera to the B/Austria, the recommended, the new recommendation is a 3a2 virus well inhibited viruses from the 3a2 subclade that does show reduced inhibition to the other viruses. Even post-vaccination sera shows that the geometric mean titers of some of the serum panels were significantly reduced against the 3a1 viruses and the 3a2 viruses.

And the anti-viral susceptibility, again, thank goodness, we're in good shape there. All viruses analyzed showed normal susceptibility to the neuraminidase and endonuclease inhibitors. And I'm

gonna end with some acknowledgements of our WHO Collaborating Centers in Bei Jing, Melbourne, London Tokyo, and as well as the WHO Geneva staff. This, of course, is built on the foundation of GISRS without which, you know, that's about 180 laboratories globally that serve as National Influenza Centers without which we couldn't do any of this work. And they are the boots on the ground.

And they've also done this all while being very instrumental in the Covid pandemic as most of those GISRS laboratories are detecting SARS Coronavirus-2 and analyzing it. Our partners at the University of Cambridge. I list those on the slides and they do the cartography. The Essential Regulatory Laboratories, U.S. partners, the Association for Public Health Laboratories, United States Air Force School of Aerospace Medicine, USAFSAM as we like to say, Naval Health Research Center.

And then fitness forecasting. I didn't show you any data from the fitness forecasting partners this go round. But they're really led by two teams, two

different groups, Michael Lässig and Marta Łuksza, as well as Trevor Bedford and Richard Neher in a different group. And then all of our CDC Influenza Division staff. Special thanks to Becky Kondor, who's the deputy director of our Collaborating Center, Min Levine, who helps a lot with the human serology, particularly the H3.

Larisa Gubareva works on all the antiviral resistance as well as NA antigenicity, and John Steel who runs the team that does a lot of antigenic characterization of all the seasonal viruses. And with that I will end with a disclaimer from the CDC. Thank you, very much.

DR. HANA EL SAHLY: Thank you, Dr. Wentworth. I am putting your video on. I have a couple of quick questions to get us started. So for the southern hemisphere influenza virus vaccine, H3 (audio skip) which seems to cross-neutralize or the sera seems to (audio skip) 2a1 better than the other way around. Did I catch that right?

DR. DAVID WENTWORTH: So you're talking about

the H3, right? So it's the 2a1 vaccine sera seems to cross-neutralize against the 2a2, and particularly the other clades, a little bit better than the 2a2 virus does against the 2a1 or particularly the other clades, the 1a and the 1b. Now we know the 1a and the 1b are declining but they still circulate. And so it's kind of an important point just to see, you know, partly why these strains are selected.

And the Cambodia strain, you know, that's going into our arms this fall, or up our noses if it's live attenuated, is really nice in the fact that it really protects well against 1a and 1b viruses, as well as the 2a1 viruses which it comes from. And shows some cross-protection against the 2a2. Whereas we're still seeing an increase in that 2a2 viruses. And the anticipation is, six months from now in the southern hemisphere they'll be displacing the 2a1 viruses.

And so that's why, while they may not have as much breadth in their antigenic cross-reactivity backwards in time, it's a little bit safer because they represent the most divergent antigenically group that's

emerging, right. So you have to weigh that balance, I think.

DR. HANA EL SAHLY: And then the year before they got the Washington, right?

DR. DAVID WENTWORTH: Yeah, so for the 3a, for the H3 viruses the year before in the southern hemisphere it was the Hong Kong/45-like virus. So that one was the same for both the northern and the southern hemisphere. And the one that was different between the northern and the southern hemisphere was the H1. And the H1 viruses being the more updated one being given in the southern hemisphere. And that's the same one that's in our vaccine this fall for the H1.

DR. HANA EL SAHLY: And compared to the --

DR. DAVID WENTWORTH: It's four different groups and it's quite -- sorry, that it's like that but we have a lot to do in this hour.

DR. HANA EL SAHLY: So are we seeing -- in the fall of 2021 are we seeing a higher number of isolates compared to the fall of 2020 for --

DR. DAVID WENTWORTH: Yeah, that's a great

question. It's just a -- I would say just slightly higher so far. Not a lot higher yet. You know, we've been watching very closely. There's been ILI, influenza like activity happening, but a lot of that I think has been driven by both rhinovirus and RSV. And we are starting to see more viruses coming into the -- each of the state public health labs and then they're being forwarded on to the CDC now. And they do represent quite a few different viruses.

Like we're getting H3, not too many H1, and B viruses, B/Victoria viruses. So it appears -- it appears a little bit more than last fall at this time, I would say.

DR. HANA EL SAHLY: Yeah. That's how I gathered but I wanted your opinion. One of the earlier slides you've shown, did I get it also correctly that it seems that H3 and 2 have increasing in proportion although the absolute remains a B as the prevalent or the --

DR. DAVID WENTWORTH: Yeah. That one it's very tricky to work out because there's such regional

differences, country differences. So, for example, China really didn't have any H3 or H1, but they just had so much B virus. So when you do that whole global thing it gets quite diluted in what's predominating. Even if you do it by hemisphere. But anyway, I think we're seeing that the H3 viruses -- I mean, where they were, they caused pretty significant epidemics. Like Cambodia had a pretty significant epidemic, you know, in the late spring.

And Bangladesh and India and Nepal seeing quite a bit of H3 now and India also seeing some H1 in multiple provinces in the north and the south.

DR. HANA EL SAHLY: So we have a few raised hands. Dr. Hayley Gans.

DR. DAVID WENTWORTH: Hi, Hayley.

DR. HAYLEY GANS: Hi. Thank you, thank you so much. I just had a couple of questions. One question, it doesn't seem like you have any data coming out of South America at all. Like even some of the larger countries like Brazil which might be very relevant to the discussion today. That's one question. The other

question -- I'll just say three questions and you can answer them as you want. So, the lack of data from South America. It also looked like when you had, at least for the H1N1 where you actually had sera from the southern hemisphere, but it was all in adults.

So I didn't see any pediatric related data and updated sera to that. So I just wondered about that. And then the third question I think related to H3, or maybe it was in the B, where there was very much an age dependent antigen. So where there was some reduced GMT it looked like it was all in the pediatric population. Actually, I think this is now to the B. And I just wondered about that too and if we're not hitting it right maybe for the pediatric population?

DR. DAVID WENTWORTH: Thank you, very much for your question. So make sure I hit them all and if I don't, remind me. So with regard to the southern hemisphere. You might remember that graph I showed where in the northern hemisphere we were getting viruses still on the Y-axis of being in the hundreds, and in the southern hemisphere it was in the tens, like

10, 20, 40, weekly. And most of those were coming more from like Australia and their catchment area than in South America.

We really just didn't have any viruses from South America to look at in this period. And we're pretty -- I mean, basically, you know, when you think of influenza viruses circulating, it's a big iceberg and we only see the tip. And with the Covid pandemic it's like the iceberg went down and little bit more. And in some parts, you know, some parts of the world we really just didn't, you know, we didn't see any. And it's whether, you know, the surveillance, some of it impacted negatively -- influenza surveillance, some impacted negatively by, you know, people working hard on SARS Coronavirus-2, or Covid-19.

And some of it just because potentially all the mitigation and potential viral interference between the viruses really reducing influenza circulation. So we just didn't have -- while the PAHO network of WHO, that region, really worked hard to test, we didn't have positives that we could analyze in this time period.

So we often get viruses and sometimes they're delayed. We've also had a lot of shipping issues. So we have to do things -- when we're talking about what we're trying to make decisions on, we're very particular about the collection dates of the swabs that we're analyzing.

We have some -- we have received some materials from the PAHO region but they were really earlier viruses, prior to February. Anyway, so there's that piece. The second piece was, I think the serology in the pediatric population. And you're right, it was the influenza B. And it's always that pediatric population where you can see antigenic distinction a little bit easier than in other populations. And the reason is, is our younger populations haven't been infected naturally as frequently, nor have they often been vaccinated as frequency, right.

So they don't have as much memory and cross-reactive antibodies that come up when they're immunized. And so really that's what you're seeing there. And as you point out, the pediatric population is a very important consideration in our vaccine

viruses. What we do know is in general the influenza B antigens do produce a little bit more cross-reactive response than the influence A antigens and so -- even in our pediatric population. And so, it's really a tricky business to select that vaccine virus, particularly for that one group.

But almost any influenza B vaccine in that group kind of creates, not a huge titer, but a broader titer. And so 3a2 is just as good as 3a1 and probably both are better than like an older B/Washington type in that population with the assessment of the committee. And then your third question I may have forgotten already. I apologize.

DR. HAYLEY GANS: No, no problem at all. I was just curious, because it didn't seem like there was any pediatric data from your southern hemisphere --

DR. DAVID WENTWORTH: Oh, yeah, yeah, yeah. So we --

DR. HAYLEY GANS: -- sera that you were able to obtain for the --

DR. DAVID WENTWORTH: Yeah, yeah. We don't

get sera -- so that serum, that's collected in Australia, from their population. And we get it from the WHO Collaborative Center in Australia. They ship it to us and then we can test it. They don't get as much sera from that age group. So they have a higher age groups that they get sera from. And you can see, the U.S., we've really invest a lot in serum in part as a response to VRBPAC wanting to see more data in sera. So we have many different age groups slices in the U.S. serum channels.

DR. HAYLEY GANS: Got it.

DR. DAVID WENTWORTH: And so, it kind of points that out for some of the other serum channels that we have available. We just don't have --

DR. HAYLEY GANS: Thank you.

DR. DAVID WENTWORTH: We just don't have access to those is the basic, short answer to that question.

DR. HANA EL SAHLY: Thank you, Dr. Gans. Dr. Paul Spearman.

DR. PAUL SPEARMAN: Hi, thank you very much

for that presentation. As usual a lot of data to see and many slides. But it seems to back up the choices for the southern hemisphere, the changes. So I think that really seems to be very logical. But my question is more about vaccine strategy as we go forward with -- especially in regard to the B/Yamagata, you know, inclusion in quadrivalent vaccine. How much value is that really giving us now with very, very little circulating Yamagata?

And is it -- would it even be possible to, for instance, instead include two subclade members of H3N2 with all the diversity going on there? And wouldn't we end up protecting more individuals from hospitalization and death?

DR. DAVID WENTWORTH: Right. I think that's a great question and something that we are, you know, actively discussing. So let's just talk about -- well, I'll take the B/Yamagata piece first. We have an opportunity here partly driven by, you know, hugely different B/Victoria viruses emerging and disseminating globally, likely inducing a lot of cross-protection,

acting as kind of a natural vaccine against Yamagata. So this is now me waving my hands. I mean, it's a bit of a hypothesis. But we have an opportunity with Yamagata being so low.

But remember, there were detections, we just -- they were very high CT values and our viruses couldn't be isolated. So during this time period there were detections of B/Yamagata. And of course, we don't know all the viruses circulating in all the people. And we have already started discussions within the WHO of, well, what's the timeline of a Yamagata vaccine if we can really illustrate that none have been detected over a period of time, right. But the idea would be you want to keep it in the vaccine because we have an opportunity to eliminate it, right, as a pathogen.

So we went to keep it in the vaccine, number one. So in quadrivalent vaccines, B/Yamagata should be in there. You can the trivalent is used in many, you know, in the U.S. we use mostly quadrivalent vaccines. But you can see trivalent is still recommended and used in many parts to the world. So right now, that's not

even included in the trivalent. So we'll see how well the B/Victoria helps induce cross-protection against that Yamagata there. And so there's that one piece, keep it in the vaccine. I really do like the idea of -- you know, we have now manufacturing capacity for four different antigens in the vaccine.

And so the potential to put two antigens of a subtype, particularly H3 which has that huge diversity that we're always struggling with, is great. And I think -- but we do need a number of things to happen. We need studies in animals and -- pre-clinical studies in animals, some clinical studies in humans looking at, well, if we put two H3's in there is one immunodominant and the other one nothing? You know, do we do no harm, do we get a synergistic impact or an additive impact? So those studies really haven't been done.

And so that's going to need to happen. And then there's some of the regulatory pieces that my FDA colleagues can tell us. But, you know, we all think probably a little too simplistically about it. That it's a great idea and we need to investigate it but it

can't be done instantly.

DR. PAUL SPEARMAN: Right. No, thank you. I didn't think about eliminating Yamagata. That's really a good point.

DR. HANA EL SAHLY: I understand the issue of it cannot be done instantly. But I must say that issue appears, you know, resurfaces almost every -- after every flu season. And I propose this in different circles.

DR. DAVID WENTWORTH: Good.

DR. HANA EL SAHLY: And I'm not getting much traction, at least to begin the studies, you know. We have some animal data with multiclade H5, multiclade H2N2. At least in animal data looks good but (audio skip) H3N2 in animals and then humans was (audio skip). I hope someone is listening and we can get some tractions.

DR. DAVID WENTWORTH: Yeah, there's great opportunity there. I agree with you.

DR. HANA EL SAHLY: Dr. Michael Kurilla.

DR. MICHAEL KURILLA: Thank you. David, I'm -

- you may have said this and I missed it. But I'm curious about the source of the human sera that you're -- that you used for testing. Because there -- is it an aggregate of total population or is it distinguishing between people who were vaccinated the previous year versus people who were not vaccinated? And in the vaccinated sense, is it distinguishing between people who are habitually vaccinated every year versus those who are occasionally?

We have seen examples of where people who are vaccinated year after year after year display still adequate but reduced responses to those vaccines. So I'm wondering how that is done and whether or not we really have a true overview of what the population susceptibility could be to the new circulating strains.

DR. DAVID WENTWORTH: Yeah, great question. Thank you very much. So we get serum from two different vaccine platforms, or really three sometimes. We have serum from people vaccinated with the egg-based -- well, four. Egg-based vaccines, both high dose and regular, so the elderly population, some of which get

the high dose. Then we also get people -- recipients of flu cell vax. And in some years, we can even get recipients of flu blog.

Now, what we don't have is part of your question, a very good question, is it's really just a cross-section of our population that was willing to get vaccinated that year with that particular product that I just described, right. And so, it's a little bit convenient, right. So you have to be able to get the sera very early. Or actually just, you know, we'll be collecting that sera, it'll start, but people are enrolled now. And so, we want to get it as early as possible so that we can actually use it before the next strain selection.

And so we don't have great data on whether or not they were vaccinated before. We don't know -- there certainly -- I don't treat it as a cross-section of our population's immunity. That would need a different type of study where we're really looking at non-vaccinated people. So one of the key questions, you know, it's always good to think about what's the

question we're trying to address. The question that we're trying to address is whether or not the vaccine that we gave last time around has -- works, you know, neutralizes most of the viruses pretty well or doesn't.

And then of the viruses that it doesn't, are those likely to increase proportionally or not? So are they old viruses, are they new viruses, are they very rare viruses? And so I think you raise a lot of great questions. They take a different type of study than we're doing to answer, to address some of those questions. And even the question about, you know, repeated vaccination and reduced response. I think that one it would be really fun to go into some detail about that. But people talk about that reduced response and I think a little bit incorrectly sometimes.

Because -- so for example, maybe the first time you're vaccinated you go from a titer of say 40 to 320. And then next year I get vaccinated and my baseline might be 160. And so I only go up to 320 or 640. And they say, well that increase is reduced

compared to the increase that I had the first time I was vaccinated. But that's obvious. Like, that's what's gonna happen. And so I think there's some studies that literally show somewhat of a decline in titer. And so that's the more important thing to try to wrestle with.

But I don't -- I think a lot of them are looking at a reduced increase rather than a reduction in long titer. Because one of the key important things, and I will show this again next time we meet when we'll have a little bit more time, is that almost any vaccination, you know, in our hands with the serum that we get increases the titer of these flows, you know the raw titer from their baseline. And against all of the different viruses that we're testing. And so that's why we use this geometric mean titer business to look at the reductions comparatively, right.

And so what I'm trying to say there is, like even a vaccine against the Hong Kong/45 does increase neutralization against these really recent viruses. And it brings some people from 20 to above 80 in their

titer. And so that's still considered protective, you know, when you look at the correlates of protection of flu. And so, in part we're using that very sensitive assay on the human sera with statistics to illustrate, you know, because we have such poly clonal response there is a reduction to this group.

Anyway, it gets a little bit beyond -- those kinds of studies that I just described are a little bit beyond what we do for vaccine strain selection remembering the question.

DR. HANA EL SAHLY: Thank you, Dr. Kurilla. Dr. Holly Janes.

DR. HOLLY JANES: Thank you. I wanted to probe a little bit further and follow up on one of the questions Dr. Gans raised around kind of the geographic representativeness of the viruses that you have and those that are characterized. You know, I remember one the groups of viruses you showed had a great predominance of viruses from China, for example. And other regions that were not represented at all.

So I'm wondering, can you elaborate on, you

know, to what extent CDC and WHO and this network can, you know -- or attempt to be more active with regard to capture of viruses in a fashion that is representative of the geographic diversity in viruses? And represents them, you know, seeks to attempt to represent them proportional to their frequency in terms of distribution as opposed to passive capture.

And obviously this is of greater importance in the context of Covid where, as you mentioned, you know, there's greater potential for kind of missing capture of viruses in certain geographic regions that are overburdened, you know, due to the pandemic. So to what extent is there effort to attempt to generate kind of a fair representation of the viruses that are characterized? So that we can, you know, accurately assess, you know, when there's an apparent diminution in neutralization?

Whether that, you know, representative of diminution in terms of southern hemisphere viruses at large versus, you know, just those that are more frequently characterized in your slides?

DR. DAVID WENTWORTH: Yeah, you guys are bringing up very good points. So this one actually we're doing a lot on this more with the WHO and the CDC directly. So I'll try to walk through a few things. One, this is a very unusual time where we're not seeing as many viruses. Normally we see the viruses move geographically very rapidly. We don't have these pockets of evolution that happen. And kind of like I was saying about Western Africa, Togo, we're not sure if the viruses there will really disseminate, for example.

But we were -- there is great surveillance there, active infections, and we were getting viruses. So there's just not as many flu viruses around. And I tried to make that point by saying the GISRS is testing 150,000 specimens weekly and not finding positives. So that's -- it's true that there's just not as much virus around. So it's a very unusual time. But beyond that, we've been -- for many years now both the WHO and the CDC have been trying to strengthen the GISRS network by doing more training on detection across many countries.

We, in the United States and the WHO, help support distribution of reagents and protocols for detection in real time PCR in part to all the national influenza centers globally through something called the International Reagent Resources. It used to be called the Influenza Reagent Resource but it became international with SARS because we're distributing reagents for SARS as well through that mechanism. And so what that does is it provides real time PCR kits toward all the national influenza centers.

So many per month so they can continually survey through a different -- obviously different countries have different approaches for surveillance. Like, you know, some use a hospital network, some will use more outpatient physician networks, et cetera. But that doesn't really matter for flu. The most important part is regular surveillance in that network and continuous month, month, month, month. And so, detection.

And then we also developed, last year -- because we knew a lot of testing for SARS was

happening, and some at the expense of flu, the CDC developed something called Flu- SC2 Real-Time-PCR method which we publish now. This simultaneously detects influenza A, influenza B, SARS Coronavirus-2, and has an internal housekeeping gene in it, you know, a human gene target in it. So it's a quadruplex that you can just run one assay on and detect all three of those pathogens.

And so you can detect co-infections better and you can just distinguish between flu and SARS very rapidly in the same test. And that's also being distributed through the IRR so that people testing regularly for SARS can also see flu there. So you'd pick up flu that might go in the trash can, so to speak. So that's happened. The WHO supports all of this through a lot of training efforts, regional training efforts for different -- like we did a training in PAHO on that flu SC2, we've done a training in the EMRO region on the flu SC2.

And then we're also working in the genomic space to be bringing genetic sequencing closer to the

swab, so to speak. So having -- really disseminating that ability. So that's really going to happen a lot in the next couple of years synergizing with what's been happening with SARS. I hope that kind of addresses your question. But we also have, within CDC, I should mention, something that we're calling the Deep and WIDE project. So we always have done more wide like with lots of different countries small amounts of virus everywhere.

But we are developing programs where in certain regions in the world where we know there's a lot of influenza transmission happening, and maybe year-round, we do many more sample per month. And, for example, Bangladesh is one of our sites. And that's why you're seeing some of these Bangladesh viruses. You may remember the last VRBPAC we had a Bangladesh 2a2 virus, you know, as one of our refence antigens. So that was the whole, you know, that gave us a little window on these -- before these 2a2 viruses really got more highly prevalent, a little window on that ahead of time.

DR. HANA EL SAHLY: The time is up but we can take last two questions. We have Dr. Portnoy.

DR. JAY PORTNOY: Thank you. Two questions. Number one, we were talking about removing the Yamagata strain to make room for another strain. Is there some intrinsic limit to the number of strains that can go in there? There's some reason why we can't have a, like a pentavalent virus or more strains added to the influenza vaccine? And my other question is what has the progress been on converting some of these over to a messenger RNA platform for developing vaccines?

DR. DAVID WENTWORTH: Yeah, very exciting times. Again, another maybe potential silver lining of the very bad SARS pandemic, right. So the intrinsic limit -- I don't, you know, this kind of gets out of my area, right, but I'll just comment on it. There's two -- I always bring up the regulatory. So now if you go with say, you know, pentavalent or something, decavalent vaccine, you would need to be able to produce in the timeframe that's needed. So that goes to how you provide the vaccine and how many vaccines

you're going to produce.

And then importantly you would need the studies to show, just like we did when the quadrivalent was developed, it didn't hurt the other antigens in there to add more, right. And I kind of alluded to that with just the two H3's which is rather simple. You get to a pentavalent or a decavalent you got more of those questions. Now certainly, some vaccine platforms may be more amendable to this and that -- those studies need to happen. Not just MRA but other vaccine platforms.

But one of the issues now is really if you talk with the manufacturers -- again, a little bit outside of my range but I'll comment on it. They pretty much race from the time the vaccine is made until the vials are filled and given to people to get those four batches done, right. So right now, the manufacturing window is about as tight as it can be to manufacture. You know, it's not just one vaccine, it's not just SARS Coronavirus-2, it's H1, H3, B/Yam and B/Vic all at the same kind of concentration, right.

So they basically are often doing two of the vaccine viruses at risk before the meeting is even named in order to meet the demands for fall and have it all be vialed and be able to be distributed in October, September/October. So I think there is -- but that's the classic technology of egg-based vaccines or the cell-based vaccine. I'm not quite sure about the recombinant vaccine what, you know, what their scale up could be as far as multi-valency and what their turnaround time is.

And certainly, there's a lot of effort in mRNA vaccines, for example, or nucleic acid vaccines. And there have been effort in flu already, prior to SARS Coronavirus, looking at these technologies. So I'm very excited about that because I do think that would be, you know, potentially if the titers could get as high as we get titers for SARS Coronavirus that's a very good thing for flu vaccine. And then also the multivalency has potential as well as some maybe designed molecule potential is very important.

So I think a lot of potential.

DR. JAY PORTNOY: Yeah. The other thing though is that because it's made through mRNA the protein is produced internally to the cell, which intrinsically could create a much better immune response than something that's administered exogenously like the vaccines currently are. Well, thank you.

DR. DAVID WENTWORTH: You're welcome. Yeah, very good point.

DR. HANA EL SAHLY: Our last question comes from Dr. Meissner. Dr. Meissner. Dr. Meissner. You are on mute, Dr. Meissner.

MR. MICHAEL KACZYNSKI: There you go, Cody. You're unmuted. Cody, you got your own phone muted.

DR. CODY MEISSNER: I'm sorry.

DR. DAVID WENTWORTH: Oh, there we go.

MR. MICHAEL KACZYNSKI: There you go.

DR. CODY MEISSNER: Okay, thank you. I wondered if you could comment a little bit more on your thoughts about why influenza didn't circulate to a better extent during this pandemic period? What was it? You mentioned less travel and non-pharmacologic

interventions. Do you think there's a -- might be a virus/virus interaction between Coronavirus and the influenza viruses? And the reason I was -- I mean, I was thinking about, we worry about the Coronavirus in the sense that more people who become infected, the greater the likelihood that there will be mutations and new variants will emerge.

And if there was so much less influenza virus replication or infections this past season, do you think that might have an impact on the development of new strains? Recognizing that Coronaviruses are a linear RNA and basically influenza viruses are segmented. But is that an issue with influenza as well?

DR. DAVID WENTWORTH: Yeah. I mean, so I'll just try to address that. It's a very good question. So I think undoubtedly a lot of mitigation factors really helped to reduce the influenza virus. And the travel restrictions helped to reduce global dissemination. And so that's why we saw these pockets of evolution that we don't normally see. You know,

even, for example, I really pointed out the influenza B viruses, those 3a1's really evolved in China. They then didn't disseminate much from China. And we did see them periodically in other places but they weren't as successful.

And so, we saw detections but they didn't continue on. So there's clearly those mitigation factors that we know helped suppress SARS. It doesn't feel like it because we had a pandemic. But I can only imagine what it would have been like had we not had those mitigation factors, right. So I think that that is probably an important point. And then on top of that mitigation, you know, masks and hand washing and things like that, you do have natural immunity to the flu that you don't have against the SARS Coronavirus.

And so, as I mentioned, you know, you already have antibodies that cross-react with the very newest strains. You just don't have very high levels of them. And you certainly have antibodies and CTL responses to many parts of the virus that diminish replication once it actually infects you, you know? So there's kind of

the -- I envision it as a layering. You've got a mask and you have immunity, you're less likely to catch flu because you're now reducing the chances of being in contact with the virus.

And then when you are in contact with it you already have some level of immunity. There's that piece. I do think, you know, a lot of research needs to be done on the viral interference piece. Clearly the viruses are very distinct from each other. And neutralizing type antibodies won't cross-react between SARS Coronavirus-2 and flu. But that's not to say that you don't have some parts of the nuclei caps in protein of SARS and the nuclea, you know, and the nucleal protein of flu, both of which are designed to bind RNA and have very similar features.

Some CTL responses could cross-react to that, et cetera. So you could kind of envision it's a pathogen, there's some cross-protective natures there. I think also probably what's likely is a bit of innate immunity. So if you're infected, you know, with SARS before the flu infection, say two weeks before flu, you

still have a little bit higher level of an immune response altogether. So I think I'm pretty much hand waving here. But I do think it's probably more than just the mitigation. There's something about the sweep of a pandemic virus that suppressed influenza a little bit.

DR. CODY MEISSNER: Thank you.

DR. HANA EL SAHLY: Also, school aged children are home and they are kind of the engine every year. They've been home for a while. Okay. Well, that was last question. Thank you all for your attention and thank you, Dr. Wentworth, for walking us through these complex data every year or every (audio skip). We will be on a 10-minute break. So it's now 1:20 eastern. We will be reconvening at 1:30 eastern.

[BREAK]

OPEN PUBLIC HEARING - NO REGISTERED SPEAKERS

DR. HANA EL SAHLY: Welcome back, everyone,

for the continuation of our Topic II meeting. The next session is designated for the Open Public Hearing; however, no one registered in advance for this particular session. So we will be moving with the Committee Discussion session.

COMMITTEE DISCUSSION, RECOMMENDATIONS AND VOTE

DR. HANA EL SAHLY: I want to encourage everyone to contribute to the discussion. We will be discussing the southern hemisphere influenza virus strains selection, which was so aptly described a little while ago by Dr. Wentworth. To sum it up, two strain changes have occurred between last year and this year southern hemisphere vaccine. Namely the H3N2, which continues to diversify within the a1b. And it's now 2a2, which is now included as the prototype Darwin strain. And the Influenza B/Victoria, which is now changed from Washington to Austria. (Audio skip) account for the diversification observed within the Victoria lineage.

And it's hard to predict what's going to happen in terms of circulation, but schools are back, people are letting down their guard. As we heard just a minute ago, people are travelling more often. So the importance of the influenza vaccination and following the strain diversification for current and future recommendations are all the more important.

I have no particular comment, except distilling some of the soft process that went on with this (audio skip) vaccine. No antigen more than H1, H3, N2 that keep being brought up to the surface (audio skip) twice a year. The issue of neuraminidase contribution and neuraminidase updates to vaccines. (audio skip) horizon; however, these are all research questions are kind of beyond (audio skip) our goal today. I have no particular concern given the data described (audio skip).

I will go around the virtual table, and ask my colleagues to comment, or ask questions, or final thoughts before we move on to the voting. And I'm going to go down the list as it appears on my computer,

Dr. Amanda Cohn. Dr. Cohn, can you hear me? Okay we will circle back. Dr. Andrea Shane.

MR. MICHAEL KACZYNSKI: Dr. Shane is connecting her audio, so give it a second. We'll just keep going down the list. To the members, we're going to go right down alphabetically. So, just that you know so Dr. El Sahly can call on you. All right. Take it away, Dr. El Sahly.

DR. HANA EL SAHLY: Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: I do not have any concerns with the selection of the strains for the southern hemisphere vaccine.

DR. HANA EL SAHLY: Thank you. Dr. Cody Meissner,

DR. CODY MEISSNER: Thanks, Hana. I concur and I think that the selections of the strains for the southern hemisphere are as reasonable as can be made at this time. And hopefully we'll get the right strains. So, if we're voting, I vote for it.

DR. HANA EL SAHLY: Thank you, Dr. Meissner. Dr. Geeta Swamy.

DR. GEETA SWAMY: Dr. El Sahly, I don't have anything to add and I don't have any concerns about the recommendation.

DR. HANA EL SAHLY: Thank you. Dr. Hayley Gans.

DR. HAYLEY GANS: Thank you. I think that this has been a really robust conversation. And I would say I don't have any concerns from what we know. It was only because southern hemisphere unfortunately we don't have strains necessarily from places that we're worried about. But hopefully with the data we have we're getting the (audio skip).

DR. HANA EL SAHLY: Dr. Holly Janes.

DR. HOLLY JANES: Thank you. I just wanted to thank Dr. Wentworth for his presentation and for the discussion he led. It's been very insightful. And given the challenges with anticipating the future over the coming year, I don't have any concerns. It's a challenging circumstance to forecast, and I think the recommendation is the best we can do.

DR. HANA EL SAHLY: Thank you, Holly. Dr. Jay

Portnoy.

DR. JAY PORTNOY: Thank you. I've also enjoyed the discussion. I'm overwhelmed by the amount of information that was presented; it's just mindboggling. Since there weren't very many strains of influenza last year, it's hard to predict what strains are going to be prevalent next year. You did the best you can, so I don't have any objections to the strains that are being proposed.

I am excited about the prospect of the messenger RNA platform because that a much quicker onset. It's easier to make the vaccine more quickly, manufacturing process is more rapid. So it may be possible to modify the strains quicker and more conveniently in the future once the platform is established. So I'm hoping that that will make this decision much easier in future years. Thank you.

DR. HANA EL SAHLY: Good research question, Dr. Portnoy. Dr. Michael Kurilla.

DR. MICHAEL KURILLA: Thank you. The remark is more of a question for the FDA. This is going to

be, I think because I'm rotating off VRBPAC, this will be my last flu strain selection. And, in looking at this, I really begun to wonder what advice is the FDA actually looking for from the VRBPAC in this case, because, quite frankly, the flu strains seem like a take it or leave it from the WHO. I'm not sure if there's an alternative mechanism, if VRBPAC ever voted no.

So, I'm not really sure what it is that they're really seeking from us, because it's either make these vaccines, use these strains for the vaccine, or don't make a vaccine at all. I don't know that there's any other way to do any other flu strains selection. So, that's it.

DR. HANA EL SAHLY: Dr. Gruber.

DR. MARION GRUBER: Yeah, I would like to comment on that. This is an interesting question. What I would like to say to that is that the WHO recommendations for both the southern hemisphere as well as the northern hemisphere, two strains are really, as you all know, based on global surveillance

data. And these recommendations are supposed to provide a guide to national regulatory authorities as well as the vaccine manufacturers, for the development and the production of the flu vaccine.

But the WHO also notes in their recommendation that it's the responsibility of each national regulatory authority, such as the FDA in the United States, to approve the composition and the formulation of the vaccine used in that county. So, that responsibility lies with the NRA. And of course we go by the WHO recommendations, but in the end it is an FDA decision what to approve in terms of composition and formulation. And this is why we convene the VRBPAC, to hear their recommendations and their discussions and deliberations regarding the flu bio-strains that should be included in U.S. FDA licensed influenza vaccine.

It's a bit of a challenging question for me to answer, what would we do if the VRBPAC would not recommend that. But then again I think the emphasis is really here. It's a global enterprise; it's a global collaboration to really arrive at these WHO's

recommendations every year, but again, the reason why we convene the VRBPAC is really because it lies with the individual NRAs to finally approve these flu strains. And that's my comment to the question. Thank you very much.

DR. HANA EL SAHLY: Thank you, Dr. Gruber. Dr. Myron Levine.

DR. MYRON LEVINE: Hi, I very much enjoyed this VRBPAC and this discussion. I think it's a good start on influenza virus surveillance to see so many acute respiratory specimens being examined, so few flu viruses (audio skip) particularly, and yet (audio skip) observation stand out.

One in this very large amounts (audio skip) of virus in China, and another, thinking back to 2009 when the last pandemic of flu began, when you put a world map looking at (audio skip), it was a gaping hole. And that gaping hole was (audio skip). I was so impressed today to see that there were H1 and N1 viruses, a whole aggregation of them from several countries and West Africa. So, on the global scene it's interesting to see

that.

I thought David Wentworth's explanation of the immunology of the cartography of the genomics was superlative and based on his explanations I'm very comfortable with the suggested recommendations to be made for change.

I believe this is going to be my last flu selection, virus selection meeting as well. And I'd like to thank Marion Gruber and Kathleen, and all the others and it's been great to interact with the other members of the VRBPAC and I'll miss you all.

DR. HANA EL SAHLY: Thank you, Dr. Levine. Dr. Paul Offit. And just a quick reminder to everyone that now we are gathering thoughts around what was presented. And then after the vote we will take why someone voted in one way or another. Just a little reminder. Paul?

DR. PAUL OFFIT: Thanks, Hana. I don't have anything to add other than to again thank Dr. Wentworth for just a clear and compelling presentation. It gives us the kind of information we need to make the best

decision, so, thank you.

DR. HANA EL SAHLY: Dr. Paul Spearman.

DR. PAUL SPEARMAN: Thanks, Hana. I don't have anything further to add. I think that was really strong evidence provided for choosing these strains in the face of current limitations of all the systems we have. Thanks.

DR. HANA EL SAHLY: Thanks, Paul. Dr. Paula Annunziato.

DR. PAULA ANNUNZIATO: Thank you for the opportunity to comment. As was mentioned by Dr. Wentworth, incredible amount of coordination is required between these surveillance networks for influenza, the researchers, the regulatory agencies and of course the vaccine manufacturers in order to produce these life-saving vaccines on time for biannual campaigns that need to occur every year. And this committee has such an important role in this enterprise. And so, I want to thank everybody for their thoughtful consideration, their very careful comments. And, I know that everybody who's involved in

this ecosystem is listening carefully to what is being deliberated today. So, thank you very much, and especially, thank you, to Dr. Wentworth.

DR. HANA EL SAHLY: Thank you. Dr. Steven Pergam.

DR. STEVEN PERGAM: Thanks. I think I'm one of the last, so I'll try to make this brief. Obviously, Dr. Wentworth discussions are always amazingly interesting and comprehensive. And so, I think we all walk away from this being more educated about flu after every one of his talks. I have no concerns about the strain selection.

DR. HANA EL SAHLY: Dr. Amanda Cohn.

CAPT. AMANDA COHN: I just want to add my appreciation. I have no concerns about the strain selection. I'm sorry I didn't get to meet some of the members in real life, who are departing soon, but I look forward to working with you in the future. And I think this is maybe Dr. Gruber's last meeting too, for strain selection. So, I just want to send all my appreciation for her many, many years of leadership.

DR. HANA EL SAHLY: Dr. Andrea Shane.

DR. ANDREA SHANE: Thank you very much. I also just wanted to echo my appreciation for Dr. Wentworth's presentation. I really learned a tremendous amount from this one and all of the others. And I do not have any concerns with the recommendations for strain selection. Thank you.

DR. HANA EL SAHLY: Any final comments from the FDA before we proceed to the vote, or process and the vote. Kathleen, I hand this back to you for the process of voting and the vote.

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. Just as a reminder to everybody, please only vote if you are a voting member. And you'll have two minutes to cast your vote. We'll have Dr. El Sahly ready the question out loud for the record. And then once all of the votes are in, I will read all of the individual votes out loud. Dr. El Sahly, if you could read the first question, please.

DR. HANA EL SAHLY: For the composition of egg-based trivalent, 2022 southern hemisphere

formulation of influenza vaccine, does the committee recommend the inclusion of an A/Victoria/2570/2019 (H1N1)pdm09-like virus; and of an A/Darwin/9/2021 (H3N2)-like virus; inclusion of a B/Austria/1359417/2021-like virus -- (B/Victoria lineage). Yes or no?

MS. KATHLEEN HAYES: Thank you, if you could cast your votes at this time, please (long pause). Okay, looks like we have all votes in for this question. And we do have a unanimous vote with 14 out of 14 members voting yes. So I will just read the votes aloud.

Dr. Pergam voted yes.

Dr. Meissner voted yes.

Dr. Cohn voted yes.

Dr. El Sahly voted yes.

Dr. Shane voted yes.

Dr. Spearman voted yes.

Dr. Swamy voted yes.

Dr. Offit voted yes.

Dr. Gans voted yes.

Dr. Chatterjee voted yes.

Dr. Janes voted yes.

Dr. Levine voted yes.

Dr. Portnoy voted yes.

And Dr. Kurilla voted yes.

So that closes out this first voting question. And we can now move to voting question number two. Dr. El Sahly, if you could read it, please?

DR. HANA EL SAHLY: For Quadrivalent 2022 southern hemisphere formulations of influenza vaccines, does the committee recommends the inclusion of a B/Phuket/3073/2013-like virus -- (B/Yamagata lineage) -- as the second flu B strain in the vaccine.

MS. KATHLEEN HAYES: Yes, thank you. Please cast your votes now. Okay; and all votes are in for voting question number two. Again, we have a unanimous 14 out of 14 voting yes.

Dr. Pergam voted yes.

Dr. Shane voted yes.

Dr. Cohn voted yes.

Dr. El Sahly voted yes.

Dr. Portnoy voted yes.

Dr. Spearman voted yes.

Dr. Swamy voted yes.

Dr. Offit voted yes.

Dr. Gans voted yes.

Dr. Chatterjee voted yes.

Dr. Meissner voted yes.

Dr. Janes voted yes.

Dr. Levine voted yes.

And Dr. Kurilla voted yes.

So we can close out voting question number two. And I can at this point hand the meeting back over to Dr. El Sahly to go around the table for the explanation of votes. Thanks, everybody.

DR. HANA EL SAHLY: Thank you, Kathleen. So, the next item on the agenda is to discuss the rationale of our vote. I will begin. The rational for my vote are the data presented by Dr. Wentworth. They were in line with the epidemiology and (audio skip) as we know it today. Then we go around the table, Dr. Cohn.

CAPT. AMANDA COHN: My rationale is the same;

based on the data that Dr. Wentworth presented today, I voted yes.

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

DR. ANDREA SHANE: Thank you very much. I also voted to approve based on the data that we reviewed today, as well as an understanding of the epidemiology. Just as a comment, it would be wonderful to have more pediatric data as well, but obviously we're limited by the strains that we have and the access to the data that we have, so thank you very much.

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

DR. ARCHANA CHATTERJEE: Yes, I also voted to approve the current slate of selected virus, based on the data presented by Dr. Wentworth. And I have nothing else to add. Thank you.

DR. HANA EL SAHLY: Dr. Meissner.

DR. CODY MEISSNER: Thank you. I agree with what's been stated. My only hope is that we have selected the correct strains. And that we are not

forced to encounter two pandemic viruses at the same time. And, also, just commented, I look forward to seeing some effectiveness data using a test negative design, if that's possible, comparing the egg-based vaccine with recombinant and soluble influenza vaccines. Over.

DR. HANA EL SAHLY: Thank you, Dr. Meissner. Dr. Swamy.

DR. GEETA SWAMY: I voted yes based on the data as presented. And appreciate all the work of the team in order to get that.

DR. HANA EL SAHLY: Thank you, Dr. Swamy. Dr. Gans.

DR. HAYLEY GANS: Thank you. Thank you to the committee members for their wonderful conversations, obviously, Dr. Wentworth. But mostly thank you to our colleagues all around the world. That was the reason we had the data that we did. And, I too, of course, would like to put in a plug for just getting more pediatric data points, particularly serologic, as we move forward. So, our colleagues around the world who

are collecting the data hopefully can expand some of their surveillance. But, with what we have, I feel comfortable.

DR. HANA EL SAHLY: Thank you, Dr. Gans. Dr. Janes.

DR. HOLLY JANES: Thank you to the committee and the presenters. I don't have anything to add. I feel comfortable based on the data that were (audio skip) .

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

DR. JAY PORTNOY: Thank you. I also agree with the comments that were described before the data clearly supports selecting these strains, and that's why I voted the way I did. The concern about pandemic influenza that was voiced is -- my concern is that there are animal reservoirs of influenza. And in many cases influenza pandemic arises from those sources. So it's really hard to predict when that will happen. Hopefully, that won't happen when we already have another pandemic, but we'll just keep our fingers crossed. And thank you for the great conversation.

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

DR. MICHAEL KURILLA: Yeah, I think David presented a very detailed and compelling rationale for strain selection and I think it is, even with limited, limited influenza data, I think it's the best that we can do at this point. And, so, fully support it.

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

DR. MYRON LEVINE: Given the data available, the explanation of the data by Dr. Wentworth, I'm convinced that the recommendation was rational. And that is why I voted in favor.

DR. HANA EL SAHLY: Thank you, Dr. Levine. Dr. Offit.

DR. PAUL OFFIT: The rational for my decision was based on the strength of the data presented. Thank you.

DR. HANA EL SAHLY: Dr. Spearman.

DR. PAUL SPEARMAN: Similarly, I voted yes because the data really supported the strain selection as presented. Thank you.

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

DR. STEVEN PERGAM: Similarly, it's based on the data that was presented and the work that went in from all of those who put that together, analyze the data and made it readily accessible by Dr. Wentworth.

I would just say that I'm very interested to see with these pockets of development of individual areas, how this will change when we come out of the pandemic. And, I think, these meetings are going to be even more interesting when we start to see strain evolution in the consorts post-pandemic. So, it'll be quite interesting to have discussions in the future.

ADJOURN MEETING

DR. HANA EL SAHLY: Thank you. I think everyone got a chance to explain the vote. I want to thank you all for your time and your contribution to the discussing and for your vote. And, I also would like to thank, Dr. Marion Gruber, for her leadership. Express my gratitude and the gratitude of millions around the country for her wisdom through all sorts of

times.

DR. MARION GRUBER: Thank you so much, Dr. El Sahly that really means a lot to me. And it was just like six months ago, even though it was many years ago, that I asked you if you could chair the VRBPAC. And I really, really thank you for your time and your insight. And I think it has been wonderful to have you and all of the members on this committee.

I do understand that many will rotate off in January, and I wanted to take the opportunity to thank you all for your time and for your insight, and really for helping the FDA to make the right decisions. So, really, your time is very much appreciated.

And I think that it's probably the last opportunity that I have to thank you all. So, again, your help is very much appreciated, and will be very much appreciated in the future. So, thank you. Bye.

DR. HANA EL SAHLY: Okay, I hand this over back to you Kathleen.

MS. KATHLEEN HAYES: Thank you, Dr. El Sahly. I would just like to echo everyone's comments thanking

the committee and speakers today for their time. I know it was a bit of an early morning this morning but thank for all of your contributions. And on that note, the meeting for today is adjourned.

[MEETING ADJOURNED FOR THE DAY]