FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
160th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Virtual Meeting

October 2, 2020

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

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OPENING REMARKS: CALL TO ORDER, INTRO OF COMMITTEE

DR. EL SAHLY: Welcome, everyone to the 160th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. This meeting is a teleconference with the topic of discussion being the strain selection of the 2021 Southern Hemisphere influenza season strain -- vaccine. I'm sorry.

We are all via a webcam now. I just want to welcome everyone and remind you to use your Raise Your Hand feature if you have a question. When you do that, we can see who raised their hand and then invite them to speak. The roll call and the housekeeping items will be now read by Kathleen Hayes.

MS. HAYES: Thank you, Dr. El Sahly. We'll begin today's meeting by taking a formal roll call. If we look at the member roster slide, we can begin with introductions with our chair, Dr. El Sahly and then we'll go in order to Dr. Beckham, Dr. Chatterjee, and so on.

When it's your turn, if you could just turn on your video camera if you'd like to state your first and last name, your area of expertise, and your organization. Then you can turn off your camera, so we can proceed to the next person. So, Dr. El Sahly, if you'd like to start us off, please go ahead.

DR. EL SAHLY: Hana El Sahly. Baylor College of Medicine at both infectious diseases and my work revolves around clinical vaccine development against influenza and other pathogens for public health matters. Dr. Beckham?

DR. BECKHAM: Hi. I'm Tammy Beckham. I'm Director of the Office of Infectious Disease and HIV/AIDS policy in the Office of the Assistant Secretary for Health.

DR. EL SAHLY: Dr. Chatterjee?

DR. CHATTERJEE: Good morning, everyone. My name is Archana Chatterjee. Everybody calls me Archie. You are welcome to do the same. I am the Dean of the Chicago Medical School and Vice President for Medical

Affairs at Rosalind Franklin University. I'm a pediatric infectious diseases specialist, and most of my career, with regard to research, has been devoted to childhood vaccines.

CAPT. COHN: Hi. This is Dr. Amanda Cohn. I am the Chief Medical Officer at the National Center for Immunizations and Respiratory Diseases. My areas of expertise include pediatrics, vaccines, and public health.

DR. GANS: Hi. I'm Hayley Gans. I am Professor of Pediatrics and Infectious Diseases at Stanford University. My area of expertise is in vaccine immunology in the pediatric host as well as immunocompromised hosts.

DR. JANES: Good morning. My name is Holly Janes. I'm a biostatistician at the Fred Hutch, and I work in vaccine trial design analysis in HIV and other pathogens.

DR. KURILLA: Mike Kurilla. I'm the Director of the Division of Clinical Innovation at the National

Center for Advancing Translational Sciences within the National Institutes of Health; background in infectious disease product development including vaccines, therapeutics, and diagnostics, and a pathologist by training.

DR. LEVINE: Good morning, everyone. This is Mike Levine. I'm the Associate Dean for Global Health Vaccinology and Infectious Diseases at the University of Maryland School of Medicine. I'm boarded in pediatrics and preventive medicine and broad vaccinology and tropical public health experience.

DR. MEISSNER: Good morning. This is Cody Meissner. My lens is not working at the moment, so I apologize for that. I'm a professor of pediatric infectious disease at Tufts University School of Medicine. I have had a long-standing interest in immunizations. Thank you.

DR. OFFIT: Yeah. Hi. I'm Paul Offit in the Division of Pediatric Infectious Disease at the Children's Hospital of Philadelphia and a professor of

Pediatrics at the University of Pennsylvania School of Medicine. My general areas of interest are vaccines and vaccine safety.

DR. PERGAM: Hello. I'm Steve Pergam, and I'm an associate professor at both the Vaccine and Infectious Disease Institute at Fred Hutchinson Cancer Research Center and at the University of Washington. My focus is on immunosuppressive population.

DR. SHANE: Good morning. I'm Andrea Shane. I'm at Emory University in Atlanta. I'm a professor of pediatric infectious diseases, and my interest is in pediatric vaccines, immunogenicity and clinical trial design. Thank you.

DR. SPEARMAN: Hi. This is Paul Spearman. Good morning, everyone. I'm the Division Chief for Infectious Diseases at Cincinnati Children's Hospital. And my expertise is in virology, in particular, HIV virology but also other viruses as well as vaccine clinical development. Thanks.

MS. HAYES: Dr. Swamy, I think you're muted.

DR. SWAMY: Sorry. I thought I -- how about now? Better?

MS. HAYES: Yes. Thank you.

DR. SWAMY: Okay. Great. Thank you. Sorry about that. Hi. Geeta Swamy. I'm an associate professor of Obstetrics and Gynecology at Duke University. My area of expertise is in maternal immunization to improve outcomes in women and young infants and running vaccine trials in this special population. Thank you.

MR. TOUBMAN: Good morning. This is Sheldon Toubman. I'm an attorney with New Haven Legal Assistance Association. I have no technical expertise relevant to this group except that I am the consumer rep or the consumer advocate for this group. Thank you.

DR. ANNUNZIATO: Good morning. I'm Paula Annunziato. I'm the Vaccines Clinical Development for Merck, and I'm the non-voting industry representative this morning.

MS. HAYES: Dr. Wentworth, since you're going to be a speaker today, if you'd like to introduce yourself.

DR. WENTWORTH: Sure. Yeah. My name is David Wentworth. I'm the Branch Chief for the Virology Surveillance and Diagnosis Branch in the Influenza Division at the CDC. I am also the director of our WHO Collaborating Center. I'm in epidemiology and virology of influenza viruses.

MS. HAYES: Thank you. And Dr. Gruber and Dr. Weir and Dr. Krause (phonetic) if you're present, if you'd like to introduce yourself, feel free to turn on your cameras and do so if you'd like.

DR. GRUBER: Well, this is Marion Gruber. I'm the Director of the Office of Vaccines Research and Review at the Center for Biologics FDA. Welcome.

DR. WEIR: Hi. This is Jerry Weir. I'm the Director of the Division of Viral Products in the Office of Vaccines at CBER.

MS. HAYES: Great. Thank you, everyone for

your introductions. I would also just like to acknowledge the presence of Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research, CBER; and Dr. Celia Witten, Deputy Center Director for CBER; and to introduce myself and just make a few administrative remarks.

My name's Kathleen Hayes. It's my pleasure to serve as a Designated Federal Officer for todays' 160th VRBPAC meeting. Christina Vert is a Designated Federal Officer as well and is also supporting this meeting. The Committee Management Specialist for today's meeting is Mr. Monique Hill, and she's supported by Ms. Joanne Lipkind. The Committee Management Officer for today's meeting is Dr. Jeannette Devine, and our Division Director is Dr. Prabhakara Atreya.

ADMINISTRATIVE ANNOUNCEMENTS, CONFLICT OF INTEREST STATEMENT

MS. HAYES: On behalf of the FDA and Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome everybody to today's virtual

meeting. The meeting is being held to discuss and make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2021 Southern Hemisphere influenza season. Today's meeting topic was described in the Federal Register Notice that was published on August 11, 2020.

The FDA CBER press media representative for today's meeting will be Megan McSeveney, and the transcriptionist is Albert Yeh. Before we begin with reading the Conflict of Interest statement, I just wanted to briefly mention a few administrative remarks and housekeeping items related to today's virtual meeting format.

For anyone using a public Yorkcast link accessible from the FDA meeting page, there's a separate link included for anyone who needs captioning. Following today's meeting, the slides will be available on our FDA meeting page; however, if you need copies of the slides beforehand, you can send an email to CBER C-B-E-R advisorycommittees@fda.hhs.gov. And for members,

speakers, FDA staff and anyone else joining us in the Adobe room, if you could just keep yourself on mute unless you're speaking to minimize feedback. And also please only turn on your video if you're presenting, commenting, or asking a question just to maintain the bandwidth levels throughout the meeting.

Lastly, if you've raised your hand and are called upon to speak on by Dr. El Sahly, please state your first and last name and speak slowly and clearly so that your comments are accurately recorded for transcription and captioning.

I will now proceed with the Conflict of Interest statement. The Food and Drug Administration is convening virtually today, October 2, 2020, for the 160th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as the Chair for today's meeting.

Today, on October 2, 2020, VRBPAC will meet in

open session to discuss and make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2020/2021 Southern Hemisphere influenza season. This topic is determined to be of particular matter involving specific parties.

With the exception of the industry representative member, all standing and temporary voting or temporary non-voting members of VRBPAC are appointed Special Government Employees, SGEs, or Regular Government Employees, RGEs, from other agencies and or subject to federal Conflict of Interest laws and regulation.

The following information on the status of this committee's compliance with Federal Ethics and Conflict of Interest laws including, but not limited to, 18 USC Section 208 being provided to participants in today's meeting to the public.

Related to the discussion at this meeting, all members, RGE and SGE consultants of this committee have been screened for potential financial conflict of

interest of their own, as well as those imputed to them including those of their spouse or minor children and for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties and primary employment. These may include interests that are currently or under negotiation.

FDA has determined that all members of this advisory committee are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to Special Government Employees or Regular Government Employees who have financial Conflicts of Interest when it is determined that the Agency's need for a Special Government Employee service outweighs the potential for a conflict of interest created by the financial interest involved. Or when the interest of a regular government employee is not so substantial as to be

deemed likely to affect the integrity of services which the government may expect from the employee.

However, based on today's agenda, and all financial interests reported by committee members and consultants, no Conflict of Interest waivers have been issued under 18 U.S. Code 208 in connection with this meeting.

Dr. Paula Annunziato is currently serving as the industry representative to this committee. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Dr. Annunziato is employed by Merck. Industry representatives act on behalf of all related industry and bring general industry perspective to the committee. Industry representatives on this committee are not screened, do not participate in any closed sessions if held and do not have voting privileges.

Mr. Sheldon Toubman is serving as a 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 are authorized to participate in the closed sessions if they are held.

Dr. David Wentworth is employed by the Center 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 the influenza virus epidemiology world-wide influenza disease burden and influenza virus vaccine. 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 respond to the clarifying questions from the

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.

At this meeting, there may be regulated industry speakers and other outside organization speakers making presentations. These participants may have financial interests associated with their employer and support from other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial relationships that they may have with any affected firms, its products, and if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any

other products or firms, not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participant needs 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. At this time, I would like to hand the meeting back over to Dr. El Sahly. Thank you. Dr. El Sahly, I think you might be muted.

DR. EL SAHLY: Thank you, Kathleen, for the introduction and the housekeeping item review. Dr. Jerry Weir, the Director of the Division of Viral Products at CBER from the FDA, is going to do the introduction of the meeting and presentation of questions. Dr. Weir.

INTRODUCTION AND PRESENTATION OF QUESTIONS

DR. WEIR: Hi. Thank you. Thanks, everyone,

and thanks for being here. Welcome.

I'm going to give just the briefest of introductions just to remind everybody what we're here today for and what we're trying to do. Many of you, if not most of you on the committee, have been through these strain selection committee meetings before, so this won't be particularly new to you. But if we go to the next slide.

The purpose of the VRBPAC committee discussion today is to make recommendations for the strains of influenza A and B viruses to be included in the 2021 Southern Hemisphere formulation of influenza vaccines licensed in the United States. Now those of you that have been through this know that we do this twice a year: One, we do it in usually late February/early March to make recommendations for the Northern Hemisphere, in other words, for our country and for manufacturers in the U.S. But we also do this second version for the Southern Hemisphere, usually about this time every year in either late September or early

October.

And the reason for this is because since 2016, we've had one U.S. vaccine manufacturer that has been approved to produce the Southern Hemisphere formulation for their vaccine. That is an egg-based vaccine and the reason I mention that is because, just to make things simpler for today, we're only going to focus on recommendations for egg-based vaccines because that's the only thing that is applicable to our discussion today.

Just like for our other VRBPAC meetings for the Northern Hemisphere, the strain recommendation and supplement approval for this Southern Hemisphere formulation follows the same process for the Northern Hemisphere. And that's why it's important that we meet so that we have officially the VRBPAC recommendation for what should be in a vaccine made by a licensed U.S. manufacturer. So that's why we're here.

What you're going to hear today is a somewhat abbreviated version of what we see for the Northern

Hemisphere when we do this in February/March. We'll only have one presentation from Dr. David Wentworth. But what you'll hear is basically the same type of information. He will tell you about the epidemiology of circulating strains from the U.S. as well as from around the world. This essentially summarized from the most recent WHO Southern Hemisphere strain selection consultation.

The type of data that will be presented, will concern the antigenic relationships among contemporary viruses in candidate vaccine strains. You'll hear about hemagglutination inhibition and virus neutralization tests using post-infection ferret sera, HI in virus neutralization tests using panels of sera from humans receiving recent inactivated influenza vaccines. I think he will probably present some antigenic cartography as well as phylogenetic analysis from HA and NA genes.

In the next three slides, I'm going to summarize the most recent recommendations and

discussions that have occurred for influenza vaccine recommendations.

About a year ago this time, on September 27, 2019, the WHO made a previous recommendation for a Southern Hemisphere for this past summer of 2020. That recommendation was that viruses to be used for egg-based trivalent influenza vaccines in the 2020 influenza season Southern Hemisphere or winter, would include an A/Brisbane/02/2018(H1N1)pandemic09-like virus, an A/South Australia/34/2019(H3N2)-like virus, a B/Washington/02/2019-like virus from the B/Victoria lineage. And in addition to those three strains for trivalent vaccines, the WHO recommended that quadrivalent vaccines containing two influenza B viruses contain the above three virus and a B/Phuket/3073/2013-like virus from the B/Yamagata lineage.

Shortly after that recommendation, this committee met and made the recommendation for U.S. manufactures of Southern Hemisphere formulations, and

that was the same as the WHO recommendation listed above on the slide. That was about a year ago in October 2019.

More recently, we had our VRBPAC meeting and WHO recommendations for the Northern Hemisphere for the 2021 season, which is coming up on us pretty soon. The WHO recommendation was made on February 28, 2020. And in that recommendation for egg-based vaccine, the following virus for recommended for trivalent influenza vaccines: an A/Guangdong-Maonan/SWL1536/2019(H1N1)pandemic-like virus, an A/Hong Kong/2671/2019(H3N2)-like virus, a B/Washington/02/2019-like virus from the B/Victoria lineage. And again, the quadrivalent vaccines containing two B viruses were recommended to contain those three viruses plus a B/Phuket/3073/2013-like virus from the B/Yamagata lineage. Our advisory committee, the VRBPAC, met and made the same recommendation on March 4, 2020.

Now, recently, just a couple of weeks ago, the

WHO met -- met virtually this time -- and made a recommendation for the upcoming Southern Hemisphere influenza vaccines for 2021. They made their recommendation on September 25, 2020, and their recommendation for egg-based trivalent vaccines for use for the 2021 Southern Hemisphere were -- these vaccines include an A/Victoria/2570/2019(H1N1)pandemic09-like virus, an A/Hong Kong/2671/2019(H3N2)-like virus, and a B/Washington/02/2019-like virus from the B/Victoria lineage. Again, for quadrivalent vaccines containing two influenza B viruses, these three virus strains were recommended as well as a B/Phuket/3073/2013-like virus from the B/Yamagata lineage virus.

Well, that's the most recent WHO recommendation. And, as I mentioned, Dr. Wentworth will go through what was behind the selection of these and recommendation of these vaccine strains.

So today, the committee is charged with discussing and making recommendations of the influenza vaccines strains that should be recommended for the

antigenic composition of the 2021 Southern Hemisphere formulation of influenza virus vaccine produced by licensed U.S. manufacturers.

To keep it simple, we're going to ask for two voting questions: One will be a vote on the composition of egg-based trivalent vaccines for the Southern Hemisphere formulation shown at the top of the slide. We're not going to go through these A, B, and C. We're just going to take one vote for the composition of the trivalent vaccine as shown here, and then a second vote for the quadrivalent Southern Hemisphere formulation to include the B/Phuket strain. And that's really all that I wanted to say for the introduction unless anyone has any specific questions.

DR. EL SAHLY: Thank you, Dr. Weir. Any questions for Dr. Weir? Can you hear me?

DR. MEISSNER: Yes. Cody Meissner. Can I ask a question?

DR. EL SAHLY: Absolutely.

DR. MEISSNER: Thank you for that

presentation, Dr. Weir. I just wanted to clarify why we're only focusing on egg based. Is that because the cell-based vaccines, the recombinant vaccine, and the live-attenuated vaccine, will not be available in the Southern Hemisphere?

DR. WEIR: Well, they're not available from U.S. manufacturers. Okay, the only U.S. manufacturer that has a license to make a Southern Hemisphere formulation is an egg-based vaccine, so I thought it would just be easier to just focus on the egg-based recommendations.

DR. MEISSNER: Thank you.

DR. WEIR: Because that's the only one it applies to.

DR. MEISSNER: Thank you.

DR. EL SAHLY: If you have additional questions, please use the Raise the Hand feature on your Adobe meet for Dr. Weir.

Okay. Seeing none, our next presenter is Dr. David Wentworth. Dr. David Wentworth is the Director

of the WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Chief of the Virology Surveillance and Diagnosis Branch Influenza Division at the Centers for Disease Control and Prevention. And he's going to educate us regarding why this decision is put forth on the table regarding these strain selections. Dr. Wentworth.

WORLD SURVEILLANCE

DR. WENTWORTH: Thank, Dr. El Sahly. I'm going to move right off of this title slide into this slide. As Dr. Weir just mentioned, we just finished our WHO Influenza Vaccine Consultation meeting. And this is really a meeting that we gathered data that's on the backbone of the Global Influenza Surveillance and Response System, or GISRS.

And a number of groups get together. The six WHO collaborating centers collect a lot of data that they've generated or have collected from National

Influenza Centers, which are called NICs, or WHO essential regulatory laboratories like the FDA, and H5 reference laboratories. These are the zoonotic groups that study all the zoonotic viruses that we're concerned about for pandemic preparedness. And I won't go into detail about that today.

As Dr. Weir just mentioned, we have these viruses that were selected, and he went over those very well. I am going to focus today -- because the real difference between this, our recommendation, and the Northern Hemisphere recommendation that we just previously discussed about six months ago, is the H1N1 recommendation. So I'm going to spend more time on the H1N1 viruses than on the other ones. But I will give you some brief information about why they were kept the same for the Southern Hemisphere.

Okay, this slide illustrates the number of specimens processed by the GISRS, or the Global Influenza Surveillance and Response System for the past number of seasons, so since 2017. You can see the

2017's a green line, 2018's the blue line, 2019's the black line and 2020 is the red line.

And what you can see is that it was having a pretty normal number of specimens processed from Week 1 through about Week 10. But then we actually saw an increase in the number of specimens being processed by our GISRS laboratories. This is in large part due to many of these laboratories added SARS coronavirus-2 testing in response to the COVID pandemic around Week 10. So you can see that spike up and then it stayed higher. And that's for, one, illustrating the level of work that they are doing. And two, illustrating that this GISRS system is very useful in pandemic settings. And it has been -- it was very helpful in the 2009 pandemic as well for flu.

This slide illustrates the circulation of influenza viruses by hemisphere from 2019 to 2020. Hopefully, you can see on your slide -- it's a little small on my screen -- but this is going from the weeks of the year of 2019 through 2020, so about Week 36 to

38 or so along the bottom of that graph.

And what you can also see there is the Northern Hemisphere's on the left and the Southern Hemisphere is on the right. The B viruses are the orange bars, and the A viruses are the blue bars. What we saw in the Northern Hemisphere was a fairly normal season, but then it actually dropped off very rapidly after Week 10. Again, that's where I've put a dashed line in the slide here illustrating when that was and when the COVID pandemic really started to kick in. And then a number of mitigation strategies started to kick in and then it did impact influenza positivity rates in the U.S. for sure. And so the virus dropped more rapidly.

And you can see on the Southern Hemisphere on the right, we've had very low levels of virus circulation over our summertime months, which is rather unusual. Usually, we see more viruses than that. The other thing is that you can see in this slide -- I probably will go into more detail later but -- with the

B viruses, the B/Victoria viruses predominated much more over the B/Yamagata virus which have been low for the past couple of seasons. And the H1N1 viruses predominated over the H3N2. And that's a little easier to see here where 70 percent of the viruses that circulated were influenza A viruses, with the majority of the influenza A viruses being the H1N1 viruses over the H3 viruses.

And then with the B viruses, the majority of those were B/Victoria viruses. And this really doesn't represent that well. And I'll go into more detail when I discuss the B virus, but they're the large majority over the B/Yamagata viruses.

So now I'm going to give you some details about the characterization of the (H1N1)pdm09 viruses. This really includes data from February through August so our most recent data. And sometimes we include more historical data for context so that you can see where we're getting some of our information from.

This slide illustrates the geographic

distribution of H1N1 viruses globally. And the color-coding on the countries and on the regions is, as you get to the warmer colors, it increases the positivity. So the very light yellow is the zero to five percent positive -- the key is down on the left over here -- whereas the red is 30 percent positive. And what you can see is that some countries, for example, in North America, the U.S.A. and in Africa, like Algeria, and Europe including Spain and Belgium, Netherlands, Ukraine reported high H1 activity during this period.

This slide focuses specifically on the H1N1 viruses detected by the GISRS system since 2017 so the past four years. You can see the red line is 2020. We had a modest year compared to 2019, but a pretty regular year compared to some of the other years like 2018. And then it pretty rapidly declined and has stayed very low since that timeframe, okay. So around Week 14, you can see it's been very, very low and even lower than we've seen in the past few seasons.

This slide illustrates the phylogenetics of

the hemagglutinin molecule, and it does a little more than that. It's a very high-level slide, so you can't see some of the details about the viruses. But I know many of you are really well aware of how this works, but I'll just briefly introduce that fact that each of these little black lines here -- you can't really make out -- are individual viruses over time. The evolution comes down this tree instead of going up trees; sometimes the evolution's going up trees. But you can see here, these are the most evolutionarily advanced viruses down at the bottom of this tree.

What we have on the right-hand side is a heat map indicating the timeframe. So these are viruses up here at the top of this heat map from 2018 timeframe, those in the middle will be 2019, and those towards the right-hand side are 2020. So you can see how the viruses are evolving through time. And then the color coding is listed here as to which region of the world they are from and also shown graphically below that.

So the most recent viruses that are

circulating currently -- if you remember in 2019, we had many clades cocirculating. And these were all clade 6B.1A -- HA -- molecules, but they range from subclades one through seven.

And what we've seen is a contraction to really three major subclades, the 6B.1A7s which are here at the top. Really the color coding over here shows you that they're really in North and South America. They're in the blue hues, and that's where we're detecting that subclade primarily. And the same is true for the 6B.1A5B subclades, so I'll call them for short 5B periodically and clade 7, subclade 7, subclade 5B. And then the vast majority of viruses circulating, particularly those circulating recently, are in this 5A subclade, which first emerged in 2019. Well, it's been around since 2018, but really started to dominate globally in 2019.

Then when we met last time and then after that, you can see this 5A subgroups that are called 5A-187 at the very bottom of this tree here -- these

viruses all in this range -- and 5A-156K. You can see how that the 187s really emerged first to dominate and spread globally. And then we started to see more of these 5A-156 viruses that are more in the blues as you can see that more in the United States and in Canada than in other regions of the world but started to disseminate further to other regions of the world. And so I took time on that because I'll be talking about these 5A groups in particular quite a bit.

The other small thing I wanted to point out is this position 156, which you can see is part of this subgroup of 5A viruses. Well, we've seen it before, this mutation occur. This occurred in late 2018 but didn't take hold. These viruses, we could tell, were antigenically distinct, but they weren't very fit or successful in the context of that HA that they were in. And at almost around the same time, a group of 156D substitutions -- so the same amino acids position -- existed, and this was in the U.S. primarily but also were not successful. But these 5A-156 viruses, you can

see how they first emerged really in late 2019 but then started to become very successful.

This slide illustrates the clade distribution globally, and it's based on sequence availability just in the data base. And what you can really take away from this slide is that the 5A viruses, which are the yellow and the red and the orange, really dominate the global picture at this point in time.

You can also take away that there are regional differences with places in Africa having some more of the progenitor 5As than anything else and not having many of the 156K viruses, but they have the 5A-187 viruses. Whereas, the U.S. has a lot of the 5A-156 viruses and 5A-187s but not many of the progenitors. That's also true in Australia. In Europe, it's more of a mixed bag where some countries having primarily 5A-187 and others having a 5A-156.

This slide illustrates the clade proportions in a little bit different way and follows it through time on the x-axis. So where I have that arrow

pointing now is North America, but then you have Oceania, Japan, Europe, East and Southeast Asia, okay. The most recent time point is on the right-hand side of these graphs, and so if I bring you up to North America, what you can see here is clade turnover over time. And so these light colored clades, again, are the 5A viruses.

And it's maybe a tad difficult to see, but at the top of that or in the middle of that are the 5A viruses. And what you can see towards the far right-hand side is the blue section, these are the 5A-156 viruses. In this red section at the bottom are the 5A-187 viruses. What you can see is that they're both increasing and pinching out the progenitor viruses that existed prior to that. And this is happening consistently, and in like Oceania it's the same situation. In Japan, really not very many of the 156K viruses and the 187s really rose rapidly, but then it started to level off and actually decrease as the 156K have increased.

And so you can see the viruses are in competition with each other and with humans. Europe's a bit of different story with very few of the 156 viruses around, and much more of the 187s displacing the older 5A progenitor clade. So that's the story there and this is complementary of Trevor Bedford and Richard Neher at Nextstrain, who are some of the fitness forecasting gurus that also participate in the meeting.

Now I'm going to tell you a little bit about the changes in these viruses. So I told you about their genetics and what we call them. On the left-hand side of this slide, you can see the hemagglutinin monomer. I'll put the arrow right over the top of it. This is an x-ray crystal structure of one monomer of the hemagglutinin. Now the hemagglutinin is a trimeric-formed molecule, so three of these come together to make a single hemagglutinin molecule on the surface of the virus. And there's about 400 of these on every particle -- primers I should say.

But each of these can be indicated by specific antigenic sites which have been mapped with monoclonal antibodies, so we have antigenic site-Sb up here at the top in kind of the purple color. That circle represents the receptor binding site, so that's where the host cell receptor and the virus connect. And so that's where the virus attaches to the host cell.

And then antigenic site-Sa, another major important site, is over here in the tan color. There's also these other antigenic sites-Ca and -Cb, and they're color coded in green and yellow, respectively.

And then on the right-hand side of the slide what I've tried to indicate is the evolution of the virus over time. So first, I mentioned we have the 6B.1A one through seven subclades. And they all had acquired mutations from what previously existed in these light blue sections. So the I295V, the S74R, and the S183P and this S183P being the dominant thing that really collected all these groups of viruses together. This happened through parallel evolutions, so multiple

branches on the tree all acquired these substitutions and then these viruses dominated. And that's what gave us the one through seven subclades.

Then, after that, we had that 5A group emerge, and so those are the blue amino acid changes. And so they're on top of these light blue changes. We have N129D shown here up near the head of the molecule, N260D and probably the biggest one, the T185I, which is up here in site-Sb. Okay.

And then beyond that, that 5A group split into two groups. It either split into the 187A group, which are shown here in green. And so you can see the pressure on the virus really in this space if you really think about it every two amino acids. First, it was S183P, then T185I, then D187A, and Q189E. And I'll show you a little different view of where those are in a minute.

And then instead of the green substitutions that are listed there, the 156K clade had these two substitutions in red. The 156K, the K130N, and then

over here the L161I, which is in the base of site-Sa.

So we have evolution of the virus really in two major antigenic sites that are different from each other. The one group of viruses really impacting the site-Sb, and another group of viruses appear to be escaping our immunity by mutating in site-Sa. It's quite a difficult system right now to deal with.

This slide illustrates looking down at the top of that trimeric molecule. So now each of those monomers have come together in the center. And you can see how maybe an antibody will try to bind to the head of this molecule. And where all those substitutions are appearing, and how they could negatively impact that previous or prior immunity. I won't belabor that slide. I just went through all those substitutions.

But you can see that over the course of a couple of years now, quite a few changes have occurred on the head of the hemagglutinin molecule. And they're all conserved in the 5A viruses. The biggest difference between the 5A-187 viruses, and the 5A-156

viruses, are the orange dots and the red dots.

And now I'm going to turn your attention to the reactivity pattern they have, as Dr. Weir mentioned, looking at antigenicity. So we look at this by immunizing animals with different viruses and, in this case, we're looking at Southern Hemisphere recommended for the 2020 viruses, the Brisbane/02-like viruses, and how well antisera to those viruses react with viruses that are circulating. This is done by the different WHO Collaborating Centers. It really shows the summary of it all is that about half of the viruses, or a little over half of the viruses, are well recognized by that antisera. But 40 percent or so are considered low, so they have eight-fold reductions in their homologous titers.

You can see it differs by different centers, and that's not really because the assay is different, it's in parts. So look at the CDC versus CNIC, which is the China National Influenza Center. Remember I showed you that China didn't have very many of those

156K viruses, and that's why they're having a high reactivity with these Brisbane-like 2 viruses.

The panel on the right really just shows the egg antigen so that we have a cell antigen and the egg antigen, so you can see the difference there. And here we don't see much of a difference between those two antigens and their ability to induce immunity that protects against the circulating strains.

And then instead of going by center, at the bottom of this slide, I've showed just the ferret antisera to the Northern Hemisphere summaries, and as Dr. Weir mentioned that Northern Hemisphere egg virus was (inaudible) Guangdong-Maonan/1536/2019. Again, we see a very similar pattern with about 60 percent or so being considered like the vaccine virus, and 40 percent low to that vaccine virus antigen.

Here is a more in-depth phylogenetic analysis of -- so it’s a little bit more granular of the (H1N1)pdm09s. What we're doing here now is integrating the antigenic information on top of the phylogeny by

color coding. And so you don't have to be able to read much about this chart, but what you can see is this top part of the tree, these are the 156K viruses that I mentioned, and the bottom part of this tree are the 187/189 group of viruses.

And then the color coding on the tips of this tree is their reactivity to a Brisbane/02-like antigen. So you can see that all of these 187 viruses react very well, and the 156 viruses are low. So, as you get to the hotter colors, you have a lower homologous titer. So it's a more reduced reactivity pattern or they're less well inhibited by antisera against the main vaccine prototype.

The heat map on the right shows many different sera, which you probably can't read the specifics about them, but one of the key sera here would be right about here right at the end of that pointer. If you follow that up, that's the Hawaii/70 sera, so that's the cell prototype for our current vaccine that we're getting this fall. And you can see it works very well against

the 5A/5B viruses, that clade seven viruses. Where it starts to fall off here towards the top half is when you get into the 156K viruses, so it has a similar pattern as we see with the Southern Hemisphere vaccine selection, the B/Brisbane.

Now this analysis here, this is antigenic analysis. So now this is getting into some very grainy detail showing you actually hemagglutination inhibition data. And again, maybe in this format, it may be challenging to see some of these titers, but I'll walk you through this pretty rapidly. What you can see on the far right-hand column here, this is antisera to the older vaccine virus California/07. So this was the first vaccine against the H1N1 pandemic that occurred in 2009.

And then the next one over is a cell antigen for Brisbane/02, and you can see that its titer is 1280. When you get down to these test antigens, if it's yellow, that's considered good, it's within the four-fold of that homologous titer. Then, as you get

into the hotter colors like the darker the orange, the dark orange is eight-fold, and the red is greater than eight-fold. And so you can see these are all greater than eight-fold. They are sliding as you go down that column.

The clade of these viruses is shown in the column to the left of that in which you can see is these top yellow ones are the 5A and the 5A-187 group, whereas the 5A-156 are escaping that antisera.

This next one over, these are 5A-187 viruses used as antigens, and this one that I highlighted is the egg, it's the Guangdong-Maonan virus. And again, you can see the same pattern. And Victoria/2454 virus, which has the same pattern.

And then we get into the 156K antigens like a Victoria/2570 cell and egg pair. And this is data from the CC at VIDRL in Melbourne, Australia. You can see how it is the opposite pattern where now the 187s aren't protected as well, and the 156s are inhibited by antisera's (inaudible) virus.

And then the final thing I'll show you -- or point out to you -- is the very last column. This is human sera that's pooled from post-vaccination sera from Australia -- so from people in Australia. And what you can see is that sera is reacting better to these the 5A and the 5A-187 viruses than it is to 156 viruses.

This illustrates pretty much the same thing. Part of the reason I have it in here -- and it is maybe not as germane to our discussion today. But it shows a cell-prototyped vaccine candidate for the 5A-156 group called Wisconsin/588. You can see here how it has a nice reactivity pattern, again, not working so great against the 187 viruses, the 5A-187 viruses, but working very well against the 5A-156K viruses. And again, not covering the 5B or the subclade seven viruses, which are in much lower proportions.

And then next to that is a qualified manufacturing cell isolate that could be used for that vaccine, Delaware/55, and it has the exact same

pattern.

Okay. So something may be a little bit easier to see on our small screens here is antigenic cartography as Dr. Weir mentioned. I will be showing you some of this as well. So this is a way to display cartographically that same HI data and collected at multiple timepoints. What we're showing you here are the color-coded dots are viruses that have been collected in the past 12 months, and their relationship to each other and to sera generated against antigens.

So down in the center of these cartographs is the Brisbane/02 egg virus. And so you can see a line pointing to that. That's right here kind of in the center of this cluster. And so anything within four squares of that is covered very well by antisera generated to that antigen.

And then we have Hawaii/70, so that's the Northern Hemisphere recommended vaccine, which again in ferrets, if you remember right, doesn't appear very different than the Brisbane/02, but we know in humans

it does. But ferrets do see this site-Sa very well, and what you can see is when we make antisera to sera, for example, the Victoria/2570 egg, this is the named vaccine candidate that was named by the WHO. That's shown right here in the egg-shaped, the large egg-shaped dot. And then the Wisconsin/588 cell is shown in the round dot.

So you can see those two are very close to each other and cover that 156K group of viruses very well. And that's basically the same thing as seen in Melbourne with the antisera that they have. Remember the U.S. and Melbourne had more of these 156K viruses to test as antigens.

Now, I'm going to turn your attention to post-vaccination human serum and that analysis. So we had a number of serum panels, the most serum panels really dedicated to H1 because human sera really recognizes differences in the H1 that sometimes the ferrets don't pick up. And so this is where you can see the divergence between ferrets and humans pretty readily.

So these panels are by age, and I'm not going to go through all the details but we have basically from 6 months old all the way through greater than 65 as you go down this graph. The vaccine virus is this kind of virus, this Idaho/07 or Brisbane/02. They're basically the same, one's the egg and one's the cell.

You can see the antisera generated when people were vaccinated with an Idaho/07-like virus, reacts very well with those viruses that are the 6B.1A viruses that had that 183P substitution. So you can see how well that vaccine does in creating antisera in all the age groups that block it.

Now, when we go to the 5A-187 group, you start seeing these warmer colors again, and this is bad news where we have the geometric mean titers getting low and becoming significant with the 90 percent confidence interval. And so you can see that with the 187 viruses. It's even more stark with the 156K viruses with many now being in the red, having really significant reductions in their geometric mean titers.

And the specific titers are indicated at the numbers in these squares, but that's not really critical. You can just use the heat map to understand this.

And this is occurring in virtually all panels in all age groups with the 156K viruses. And, for completeness, we included the 5B virus which also has shown some reductions in human sera previously, and you can see that does as well. And so all these clade five viruses are more closely related to each other than the earlier viruses that are doing the (inaudible) here.

Now, I'm going to show you this is the same type of analysis, but now using the egg-propagated antigen as the comparator. You can see, basically, it's a similar pattern except the egg antigen generates sera; or when we compare to the egg antigen, we see a few of the groups now lose some of their reactivity. And some of the reactivity gets worse with some of the other groups. But there's really not a huge difference between those two.

So to summarize the H1N1 section, these

viruses predominated in most countries in the Northern and Southern Hemispheres, and this included parts of Europe, North America, Asia, and Africa. The HA gene sequences all belong to this 6B.1A large clade, and they have subclades 5A, 5B, and 7 that are all co-circulating in different regions around the world and some co-circulating within the same countries.

The majority belonged to this 5A group or a 5A subclade, and that's further diversified into two subgroups that we are calling the 187A subgroup, which have these substitutions D187A and Q189E right in site-Sb as I showed you on the molecule. And the 5A-156K HA group, which have substitutions at 156K, L161I, K130N, and V250A, as well as a substitution in the HA2 that's unlikely to impact antigenicity. And the 156K and L161I are in that site Sa, which is up near the head of the molecule and near the receptor binding pocket.

So ferret antisera to these reference (H1N1)pdm09 viruses like the Brisbane/02 vaccine strain well recognized most of the circulating viruses --

actually the majority -- except those with HA subclade 5A-156K.

Now the post-vaccination sera collected from people vaccinated from the Northern Hemisphere 2019-2020 vaccines showed that the GMTs against -- the geometric mean titers, sorry for the acronym -- against viruses representing the various HA groups as I pointed out -- the 187A, 156K, and subclade 5B -- they were all significantly reduced. And this occurred in most of the panels, more significantly typically in the younger age groups.

The 5A-156K viruses had the lowest GMTs among all the viruses tested. I'm sorry, I don't know why that arrow sometimes shoots up there. The clade specific vaccine effectiveness estimates from 2019 and '20 were better for -- I didn't show you this data, but it's just a brief point -- that we saw better VE against the 187A viruses, particularly in the U.S., with the VE group here than in the 5A-156K viruses. And we have a lot of both of those viruses for

comparisons, so that worked out pretty well.

Of the 1382 viruses analyzed, 11 showed reduced susceptibility to one or more of the neuraminidase inhibitors, and we analyzed as well subsets of viruses for their susceptibility to baloxavir, which blocks a different protein -- the PA protein -- activity of the virus, and that also all looked good. So, from the drug standpoint, all the antivirals for the most part are working pretty well.

Now, I'm going to change to H3N2 viruses. This slide is -- now I don't have to explain it to you -- but it illustrates where H3N2 was circulating globally. And you can see there was quite a bit of activity in Europe and in parts of Africa. And we had quite of bit of H3 in some countries in Europe such as the U.K.

This slide illustrates the number of viruses, the H3N2 viruses, detected since 2018. It's a pretty similar pattern, in the red as you can see for the H1N1s, where more were detected in the early parts of

this year and it fell off pretty rapidly.

This slide is now the phylogenetic analysis. Again, very high-level view of it, and I walked you through what these maps are like. The older viruses, which still continue to circulate in some parts of the world are these 3A viruses up here. And you can see that really were only in Europe in the most recent circulation pattern.

And these did really start off in the United States with our bigger epidemic a couple of seasons back. And they're still around and still something we keep our eye very closely on because they're antigenically very different than all -- you can see this big gap here between the group here; so up here at the top, this gave rise to all the 3a viruses.

And this branch here gave rise to all the 2a viruses. And the 2a's have some subsequently evolved into multiple groups, 2a2, which really are no longer in circulation. And now the biggest group that we're tracking are the 2a1bs. And these have subdivided into

two groups, the 135K viruses and the 131 viruses, which continue to diversify into these other groups such as the 137F -- I will just shorthand named that virus periodically -- and the 197R in the 131 groups.

So the H3s tend to be the most dynamic HA evolution and are hardest for you all to keep track of these crazy acronyms. But it's our system that we have to got to have some kind of language to speak to each other about it.

This slide, the take home from it really is you can see the various colors. We really have a geographic distribution of the clades that are co-circulating. And then you can kind of just draw a Northern Hemisphere and Southern Hemisphere in your mind, looking at the picture and see how there's just so many of these 3a viruses, which are the red viruses, that circulated in Europe.

But many, many more of the 2a1b 153K viruses and their descendants such as the 135K, 137Fs and the 135K 186Ds, which are the dark green and blue dots.

And so these are the latest emerging subclades out of those 2a1b viruses, and they're very different, very distinct from the 3A, which are these red pieces of the pie. And the oldest viruses are these yellow viruses. They're kind of a plain Jane 131Ks that our vaccines used to contain.

Okay. And the 131K that I just called the plain Jane, that was the 2020 vaccine reference virus. It's called South Australia/34. You can see in the different centers how the cell-like candidate did against the viruses that were circulating with 83 percent of them being considered like that vaccine virus and 17 percent being considered low.

When we get to the egg, there was a much worse phenomenon happening here because the egg-adapted substitutions at H3 can have more pronounced impact on the antigenicity of those viruses. So you can see only two percent were considered like and 98 percent are considered low.

Now, we're looking at the reactivity patterns

to Northern Hemisphere 2020-2021 vaccine viruses, so this is in this 2a1b 135K, 137F group. So it's moved, as Dr. Weir pointed out, to Hong Kong/45. So this is actually a difference for the Southern Hemisphere recommendation than their last recommendation, but the same recommendation as for the Northern Hemisphere. So what you can see here, again, is the like with 53 percent of the total being considered like and 47 percent being considered low. And the egg differences not being quite so severe as was seen with the South Australia/34 virus, but still seeing reductions compared to these cell viruses.

This shows you the antigenic cartography. I think it's a little bit easier to understand than that very high-level view of what percentage of this virus is circulating are considered like and low over this time period. What we're really doing is looking at the most recent emerging clades because, of course, we're picking or selecting a vaccine from six months in advance. And so we have to look at these emerging

clades, which in this case are the purple dots.

These vaccine viruses shown here is the egg and the cell and cartographic data from Melbourne, the Melbourne CC. They're here, and they are covering quite well. These viruses that are purple as well as some of the blue viruses, which are this other subclade emerging from the 135K group. This is pretty consistent with data from the CC in London with the Francis Crick Institute.

You can see these three major groups. The older viruses, they're like South Australia, they're all kind of packed together here in this middle section. And then some of the newer subclades being the purple 135K viruses. And then that 3A group that's so antigenically different that was in our previous vaccine being the bright green viruses.

This slide, I haven't shown you one like this before, but this is a bit of a heat map of the phylogenic tree. It's done by some of our fitness forecasting partners. This is done really by Michael

Lassig and Marta Luksza, who collaborate on this fitness forecasting. And what it really shows -- again, are may be a little bit hard but -- the Kansas-like virus -- that's the 3a or at the top of the tree -- and some of the other evolution of the 2a viruses are going down this tree to the very bottom here.

And what's pointed out right in this square box and at this black dot is the cell version of the Northern Hemisphere recommendation Hong Kong/45. And then right here is the Hong Kong/2671, the egg candidate. So what they're showing here is the deeper reds are those that are considered more fit, and they have a higher likelihood of success in our population according to this fitness forecasting model.

And then overlaid on that on this tree on the right -- overlaid on the tree -- is antigenic analysis. So when you take antisera created to, say for example, the Hong Kong/45 cell, how well does it cover all those viruses circulating? So it does very well. It stays in these yellow, the titer reduction, yellow to orange

range for all these viruses tested that are co-circulating until you get to those 3a viruses, which are red and so antigenically distinct.

This slide illustrates some other fitness forecasting. Now this is done by Trevor Bedford and Richard Neher and their colleagues at the Nextstrain or NextFlu. You can see how, because of this bottleneck in 2020, we had all our mitigation strategies against COVID pandemic, and they are impacting influenza and decreasing its circulating. So it's a really strange year for fitness forecasting folks, because they don't have really very much data to go on in the most recent viruses. There are so few.

And so, if you look at it in one sense, if you look at the observed is in blue and then the predicted is in orange or green. And so if you predict it using one model, you can see that one group's expanding like the 131K. These are, I consider, the older viruses. But if you look at it in another model, such as the green here, the 135K group seems to be winning.

And so we really have our three major groups, the 135K, which is the clade of the previous recommended Southern Hemisphere vaccine. The 135K, which is the clade of the current recommended Southern Hemisphere vaccine that you're thinking about today. And the 3A, which was in previous recommendations of the Northern Hemisphere vaccine over here. So difficult to predict and probably multiple things will co-circulate is what we all, I think, agree upon.

So that brings us to human post vaccination sera. Here we're looking at sera from the Southern Hemisphere from Australia and Peru in adults and looking at compared to the cell geometric mean titer. And you can see that the 131Ks, that antigen is covered pretty well even by South Australia sera. We start to see reductions when you get into these 135K, 137F group, which is the current vaccine group. And more significant reduction on a very small number of viruses that have evolved an additional substitution there at 144, and then this other group here, this 135K major

subclade and the 186 substitution.

So we like to look at very specific substitutions in each of these clades to see which ones have the biggest effect. But you can see that human sera currently doesn't protect as well against any of those groups and, in this case, does poorly against the 3a. The Northern Hemisphere sera did very good against the 3a groups and better protected against the 131 groups, and I showed you that the last time we met.

For the H3N2 summary, these viruses collected February to August 2020 continued to show regional heterogeneity. The HA subclades 2a1b viruses have predominated in most countries, while clade 3a viruses predominated in just some countries in Europe.

The 2a1b viruses fall under two major subgroups that we're kind of calling the 131K and 135K groups. Then each of these can be broken down in more detail, but they are the major subclades. And with the 135K, we have this one 137F group, which is where our vaccine sits that's recommended, and that is being used

in the Northern Hemisphere this fall. And we have this other minor subgroup, this 138 group, that emerged slightly after this 137 group. Some of them share the same exact substitutions, for example, this F193S. It's in both of those, and that's in a major antigenic site. And we do see cross protection of those with ferret antisera, so that's good.

For antigenic characterization of the H3N2, the HA clade 2a1b virus subgroups were antigenically distinguishable with ferret antisera raised to the 131K egg-grown viruses inhibiting few of the recently circulating viruses very well. However, the ferret antisera raised against the 135K virus with the additional substitution at the 137F, 138S, and the 193S inhibited the major of the recent viruses. And it inhibits the 135K viruses, which are these emerging clades at the bottom of the trees, better than the older 131K groups.

The ferret antisera to the 2a1b viruses here on this slide, poorly inhibited 3a viruses. And ferret

antisera 3a viruses poorly inhibits all the 2a viruses. So that's showing clear antigenic distinction between these two co-circulating groups. The 3a viruses remain antigenically similar to the Kansas/14, the older vaccine strain used for the Northern Hemisphere. And human serology studies using serum from people vaccinated with South Australia/34-like virus illustrated that the geometric mean titers of the most recent representative cell-propagated viruses, from all the genetic groups, were significantly reduced relative to the egg-propagated South Australia-like viruses, and to varying degrees relative to the cell-propagated South Australia-like viruses. And this was particularly true for those that are in that 135K subgroup, like the Hong Kong/45.

Okay. Now I'm going to turn to influenza B viruses, and I'm going to be a little bit more brief on some of these. It's pretty good news here. We did see a lot of influenza B activity, particularly the B/Victoria virus as I mentioned earlier. And you can

see that here, and this was global.

This shows you the B viruses detected, again very similar pattern. But you can see how high the peak in 2020 was and the peak in 2018 was in the beginning of the year.

This shows you the B distribution. And I wanted to make this point better because none of the other slides illustrated this as well. And with certainly our genetic data, and the viruses that we're getting in the United States clearly indicate this. That we're really seeing a very small minority of B viruses that are B-Yamagata lineage. So, of the two B lineages, 98 percent are the B/Victoria viruses. And this shows on this side over here, the regionality to it where most of the Yamagata we're seeing are more in South America, but it's still not huge numbers.

So I'll take you through the B/Victoria viruses now. This is the phylogenetic tree. Virtually all the viruses of recent times are in this group. So the long story is the HA that existed back in this

timeframe, in 2018, didn't have a deletion in the hemagglutinin. So, rather than a substitution, these viruses evolved two different deletion series. One here which we call the double deletion mutants. So this is like our Colorado vaccine that we had previously. It had a two amino acid deletion at 162 and 163, so you can see how this would alter the antigenic makeup of the virus and it did.

And then we had the more recent viruses that all belong to this branch here, and they are the Delta 162 to 164. So now it's the exact same amino acid positions, but it's one additional amino acid deletion in that group of viruses. You can see by the dashed color coding that they are globally spread, and virtually all of them are in that category that what we call sometimes for short, the triple deletion category.

And that is what is in the Southern Hemisphere 2020 vaccine and what is being recommended for 2021. And it's the B/Washington/02-like viruses that are the cell and the egg counterpart from the left- and right-

hand side of this slide. And what you can see here is both the cell and egg work very well against virtually all the viruses circulating with 92 percent of the viruses being covered well, and really 86 percent being covered well by the egg antigen. So serum against the egg antigen neutralizing at least 86 percent of the viruses circulating very well.

I won't belabor this cartography. It's three different centers -- the Tokyo, Atlanta, and London -- all showing a very similar pattern with the purple dot being viruses that have the triple deletion, and the orange dots being those with the double deletion. You can see we had more of the double deletion viruses in the U.S. still circulating than the triple deletion, but that's been displaced now to virtually all being triple deletion.

And you can see how well these viruses are placed in -- the antigens are the large dot -- and how well they're placed against all the small dots that represent the different viruses that were tested. And

the gray -- I should have mentioned that earlier -- but the gray indicates where the older viruses that existed were circulating. So this is the older vaccine virus B/Brisbane/60, and you can see that up here. And so that's all these old viruses were like that.

The post vaccination human sera again, with B/Washington -- so now these are adults immunized with the B/Washington/02. You can see it's covering -- the virus is circulating very well. And we selected some really odd antigens that had major substitutions that are emerging groups, such as this group here and this group here. And you can see that the sera, when compared to the cell geometric mean titers, is working very well. And there is a little bit of drop in comparison when you compare it to the egg viruses, but not as significant as we see in other antigens.

So, to summarize those B/Victoria viruses, they greatly predominated over those in the Yamagata. Most of the viruses, if not nearly all, had HAs with the deletion of three amino acids in their HA protein

and additional substitutions that are known for that clade that I pointed out called G133R and K136E. The majority, 85 to 90 percent, were recognized well by ferret antisera against cell culture-propagated and the egg culture-propagated B/Washington/02-like viruses. And post-vaccination human sera recognized the current B/Victoria viruses very well for the most part, even some of the more antigenically advanced versions of those viruses.

Now to the Yamagata viruses, and here is the clade. And good news with the Yamagata viruses, it's a very boring phylogeny. You can see how flat this tree is and how the most recent viruses all are very homogeneous for the most part. We have a few long branch lines and a few odd ball viruses out there. We can also see from the time tree, it's just a very few B/Yamagata dashes that you see on the right-hand side. So, if you slide your eye down this graph, you don't see a lot of dashes. There's very few viruses circulating that are in this B/Yamagata. They're all

clade 3.

Those that are circulating and can be analyzed, do react well with the antisera generated against the named vaccine virus B/Phuket/3073 whether it's the cell antigen. And we do see some drop off with the egg antigen, you can see 89 percent going to 50 percent. But you can also see very small numbers here being able to be analyzed because so few viruses are around for this time frame.

This shows you the cartography. Again, it illustrates that same point where we have the B/Phuket cell. That's really what you focus on when you focus on the cartography and how well that antiserum would cover the currently circulating viruses which are all these small red dots here.

So, to summarize those B/Yamagata viruses, they've been detected at very low frequency. All the viruses have this clade 3 HA, which is like the B/Wisconsin/1/2010 and B/Phuket/3073 clade. The majority were recognized by ferret antisera very well

whether it was raised against cell culture-propagated or egg propagated B/Phuket, and the post-vaccination human sera recognized currently circulating B/Yamagata very, very well.

So I'll end here. I may leave this up if we have questions. This is to acknowledge all the collaborating centers and the central regulatory labs and our partners that help with this process.

DR. EL SAHLY: Thank you, Dr. Wentworth, for this tour around the world with the antigenic variability of the influenza A virus and influenza B as well.

I'm going to give time for my colleagues to prepare their questions. Those who do have a question, please use the Raise Your Hand feature so we can see your name, and Kathleen or I can call your name to ask the question.

I will begin by asking a question regarding whether the lower circulation of influenza viruses in general, that occurred as a result of the social

measures against SARS-COVID-2, have resulted in lower diversity or is that too early to tell? Is that too short of an interval of time to see any difference even?

DR. WENTWORTH: Dr. El Sahly, I think this is one of our questions as well. So we do still see diversity. It's just so -- it's hard to say how strongly you believe it because of the low numbers, you know, especially the most recent viruses.

DR. EL SAHLY: Mm-hmm.

DR. WENTWORTH: And we really are basing a lot of the data that I can show you between viruses that were really isolated between February and March because so few viruses were isolated and able to characterized April through September.

DR. EL SAHLY: Mm-hmm.

DR. WENTWORTH: And so that's where that fitness forecasting models are going up and down, just depending on the model that you used in part because they don't have a lot of sequence data to use in that

analysis from April onward. And we haven't seen -- in the U.S., we know very well that the positivity rate has gone down, and then, in some other countries, they're maybe some testing deficiencies because they're so focused on SARS testing and needs for the pandemic, of course. But, in the U.S., we've had pretty strong ability to continue testing for influenza virus, so, even if you just do it based on positivity rates, we've seen positivity rates drop significantly.

DR. EL SAHLY: Mm-hmm.

DR. WENTWORTH: And so it's a real phenomenon that the viruses aren't around as much. I'm probably not answering your question, but it's making it very difficult to know what will come through the bottleneck. Will it be the same snapshot just at lower levels that we had at the end of our seasons? Or will it be something unique that really wasn't on our radar because it's so antigenically advanced, somehow it's more successful with these mitigation strategies?

DR. EL SAHLY: Okay. All right. I guess, the

next season maybe will educate us a little more as we are continuing with the social measures.

DR. WENTWORTH: Yeah. Just to follow on that, I think, what people are considering is those that have high percentages of the population have a good chance of continuing on and generating progeny that maybe are a little bit more advanced. So what you can anticipate is some of the major groups will still be there, and they may be descendants of those groups.

DR. EL SAHLY: Okay. The other minor question I have is that -- did I catch it correctly that influenza A(H1N1), the 187 and the 156 subclades, are antigenically unrelated to a large degree?

DR. WENTWORTH: Yeah. This is really an interesting thing. So they're quite related but then become very unrelated with ferret antisera. So, when you take the ferret antisera, it really distinguishes those two viruses very well because the ferret antisera really recognizes these changes in the 156 region very well. So the ferrets tend to respond in the

immunodominant way to that site-Sa. And we did discuss that in the past VRBPACs where I showed you pediatric human sera and how it could see -- it could be used to identify changes in that site-Sb that ferrets were not seeing.

And so, when you look at the human pools, the human sera, they kind of react equally poorly with both of those groups, right. And so we don't know how -- the ferrets I think accentuate the antigenic distinction between the 156K viruses and the 187 viruses. So, I think, the ferrets are accentuating that distinction, but clearly make it -- because of the way ferrets are -- very easy to identify that that's having an antigenic impact, those 156 substitutions are.

DR. EL SAHLY: Okay. Thank you. We have few of our members with questions. We will begin with Dr. Paul Offit. Paul, would you please unmute and ask the question?

DR. OFFIT: Yes. Thank you, David. That was

a superb talk. I really appreciate that. I just have sort of a general question from my own interests. It appears that the B/Yamagata is a relatively stable virus as compared to the others. I mean, if that's the case then, if all the viruses were like B/Yamagata, could one argue you don't really need a yearly vaccine?

In other words, the reason that B/Yamagata remains low is because I was immunized not just last year with that but the year before, the year before and the year before that. In other words, if I got vaccinated five years ago against B/Yamagata, I would still be protected against B/Yamagata today. Do you understand what I'm asking?

DR. WENTWORTH: Yeah, I do understand what you're asking. I think, it's a really intriguing question, and thanks for your comments at the start of that question, Dr. Offit.

I'll tell you what I think is going on with the Yamagata. So we had two large antigenic drift variance occur from the B/Victoria lineage. First, it

was the double deletion group. That really swept the globe and really hit the U.S. pretty significantly. And you imagine, in some ways, that's like a new pandemic virus or a very good vaccine campaign.

Then we had the triple deletions come, and they are antigenically distinct from that double deletion group. And again, they've really dominated last season. We had a huge influenza B season in the United States, for example, particularly early on in the season, and it was really impacting a pretty good chunk of our population.

And so, I think what that's done is stimulated a lot of memory to the conserved regions of the HA proteins that are shared between the Yamagata and Victoria viruses. So, in effect, it acted like a vaccine against Yamagata viruses; because it was so fit and so successful, it was doing that.

Whether or not we need to remove the Yamagata from the vaccine is a whole other question. And I wouldn't agree to that right now, because some of the

Yamagata viruses that we see, the very few that we see, some of them have a number of amino acid changes, pretty distinct and odd viruses. But there's just so few of them you couldn't determine whether that would be a good vaccine or a terrible vaccine. So it's better to stay with the progenitor as the vaccine. You know, that's kind of the opinion of the committee.

If we see one of those groups start to really take hold and not be just one-off viruses, then that's when it may be smart to move to that. Because what could happen is that's a very strong bottleneck, and it could go very antigenically advanced and have a lot of B/Yamagata. And it could impact certain parts of our population more significantly than others.

DR. EL SAHLY: Hmm.

DR. WENTWORTH: But it would be great if we could wipe it out and then have only three components that we could add -- do other things with our vaccine and not disrupt manufacturing over.

DR. OFFIT: Thank you. Thanks, David.

DR. EL SAHLY: Okay. Dr. Spearman has a question. Paul, do you want to unmute yourself?

DR. SPEARMAN: Sure. Thank you very much for that presentation. There's so much data there that I know it gets gone over in lots and lots of detail at the WHO meetings.

The thing that was most striking that was very early in your talk and like Hana already asked about, the lack of a season really in the Southern Hemisphere was so striking. If you plot that out from past years, is this a historical low, because it looked like there were hardly any strains at all? And I wonder if that just means it's going to be very, very different in coming years than it has been.

DR. WENTWORTH: Yeah. The number of positives that were identified is a historical low for the GISRS. As I maybe alluded to, it's harder to tease apart whether that's due to a lot of mitigation issues related to the pandemic, or in part due to less testing for flu because health systems are so stressed testing

for SARS.

So it's easier to disentangle that in the United States than it is in other countries where we don't have as much understanding of what's happening. I'm sure over the next year, with WHO's efforts, will delve into that in more detail trying to understand how many flu tests they've done.

So, for example, for a National Influenza Center, even if they're doing testing, if they were getting negatives, they would be less likely to take the time to report it into the WHO structure that they did X number -- the denominator is hard to figure out right now. So that they did this many tests and they were negative. Because there isn't a virus there, there's not a lot of incentive to report that at the moment; they're busy reporting about COVID and all of that, so they have their hands full.

So they may even be doing the testing or at least some National Influenza Centers maybe doing quite a bit of testing. But they're also a lot of times the

same groups that are working on SARS-coronavirus-2.

DR. SPEARMAN: Sure.

DR. EL SAHLY: Okay.

DR. SPEARMAN: Thank you.

DR. EL SAHLY: We have a question from Dr. Kurilla. Mike, please unmute yourself.

DR. KURILLA: There you go. Can you hear me okay?

DR. WENTWORTH: Yeah.

DR. EL SAHLY: We can.

DR. WENTWORTH: Yep.

DR. KURILLA: Thanks a lot, David. My question is a little bit related to what Dr. Offit was getting at, but I was more intrigued by the Victoria predominance. I don't know on an absolute level relative to the A strains, but you seem to show some pretty good antiserum reactivity. I'm wondering is the predominance -- is that saying something about the lack of vaccine efficacy of the Victoria component, or is it saying something about the Victoria lineage relative to

the Yamagata that is a difference?

DR. WENTWORTH: I think it's saying something relative to the latter part of your question. So Victoria being a very unique antigenic drift variance, it's very successful really being a very fit virus as an influenza B virus; outcompeting its, basically, parents that didn't have the deletion, drastically pushing those out and basically wiping them out from detection. Very few of those around at all. And really doing a number on the other variant that evolved nearly simultaneously, which was the double deletion group and wiping it out.

So it's a very fit virus with a deletion and probably antigenically very distinct. So it's just having a much better -- it's just much more fit in our population. And it has very little to do with the vaccine because the vaccine efficacy isn't bad for that group of virus at all by our measures of vaccine efficacy. So it's really -- you know, globally, there's not as much vaccine used as it is in some

countries. So this is a phenomenon that's happening globally in all these populations that are really driving it by prior existing immunity, most due to natural infections and not the vaccine that's driving that evolution.

DR. KURILLA: Thanks.

DR. EL SAHLY: Okay. Dr. Gans. Hayley Gans has a question. Hayley, do you want to unmute yourself and ask the question?

DR. GANS: Yes. Thank you. Thanks very much, David. I really enjoyed your presentation, always full of a lot of data and that's so helpful to us in understanding that. A lot of my sort of specific clade and subclades were asked and answered, so I just have three more basic questions that I thought I just wanted you to address. I was just going to say them or would you like me to do them one at a time?

DR. WENTWORTH: Go ahead and say them.

DR. GANS: Okay. So the first one is it really looks like the majority of all of the viruses

that are being looked at are actually not subtyped, so I'm wondering if you're worried about any of the integrity of the data? Or is it just that because we're surveying throughout the whole season and there's that consistent pattern that we're not worried that we're missing some variation? And maybe even the way that majority of these infections are, because if 49 percent isn't being subtyped, we don't really actually know how those would fall out. So that's the first one.

The second one has to do with more of the fact that we're here looking at the Southern Hemisphere. I noticed at least in your geographic plots that a lot of the African countries that fall into that Southern Hemisphere didn't actually look like they had data, and so I'm not sure how to best look at that.

And then my third one is just, since we're here looking at the egg based and such, the U.S. portion, how much of the markets, considering the difference in how they perform in terms of the cell

based, is going to be the egg based versus the cell based for these communities?

DR. WENTWORTH: Okay. So, yeah, I'll work backwards. So the market, I'm not the best person to ask about the market, but more than 80 percent of the vaccines are really egg-based vaccines that are available for distribution. And so that, of course, can change based on the manufacturing and consumers and things like that. But that's about where we're at.

With regards to the Southern Hemisphere and Africa, it is really difficult now because we're not seeing very many viruses, so we don't know exactly what's going on. And it used to be historically we saw viruses kind of end in Africa. They would kind of go around the world and they would be kind of the older clades, but that's not true anymore.

We're seeing some in the West Africa that are -- you know, like for example, we do have some spots where we see in countries in western Africa where the 135K subgroup of the H3s are, for example, and they're

really related often to viruses in Asia. So viruses from Asia seem to be moving to that western African region. And so it's not likely discussed. The data's sparce, and it's very difficult for the Southern Hemisphere -- the most recent Southern Hemisphere viruses to understand what's there in prevalence.

And I think that's related a little bit to your first question which is how can we trust all this data if so few are subtyped? And so I actually have less worry about that, and that's in part because that really represents a large number of viruses. And so subsets are subtyped, and you can just kind of take those percentages and put them on all those unsubtyped viruses and you would have that kind of information.

For example, in the United States, we generate a lot of data that goes to that graph for WHO. It's listed as unsubtyped at the time because it's from the clinical laboratory system where they're just getting flu A positives, right? But they take a subset of those and they send them into the state public health

laboratories which do subtype the virus, and so we do see the percentages in the U.S. at a much more granular level. Actually, almost all those viruses are genomically characterized, either by the CDC or by our partners in the National Influenza Reference Centers that we have cooperative agreements with to do sequencing.

I think it's kind of unnerving when you look at it, and you go, oh, jeez, you know, 50 percent aren't subtyped. But there's a lot of specimens normally, and so it really represents a pretty good distribution when you see the ones that are subtyped and how many were circulating. The most difficult ones this year were the B viruses with the Yamagata being so exceptionally low. By not subtyping, you kind of disproportionalized that. Did that answer your question?

DR. GANS: Thank you.

DR. WENTWORTH: You're welcome to -- okay.

DR. GANS: Yeah.

DR. EL SAHLY: I have a follow-up question. So correct me if I'm wrong on that one. The proposed strain for the Southern Hemisphere for the H1N1 is 156K-like for lack of a better designation. And the one that we picked six months ago for the Northern Hemisphere is 187-like.

I remember that very informative, I guess, visual that you put. It seems that a lot of regions in the world were heading towards dual circulation of those two viruses. Not so much of a question as a comment, it's like we are going to be performing an experiment to see how these two choices, which are rational at the time given the data, are going to play out in terms of the relatedness and the effect on circulation. It's a very interesting situation with the H1N1 this season.

DR. WENTWORTH: Yeah. And so I guess I'll comment on that. Because if you can kind of think back to that -- I think I know what you're talking about. If the clade turnover slide by region, that slide,

which really was probably not a take home from that, is right now that 156K group represents about 30 percent of the viruses globally, right? And back when we selected the 187 group, it was much lower globally. It was probably eight percent or something like that. And we had seen those viruses before, but they never took off. So they didn't have the right substitutions in other parts of the molecule to allow them to be fit in our population, and now they do.

And so what we're projecting now with the Southern Hemisphere recommendation is that six months from now, that group will move from 30 percent to probably more than half, right? But what's going to circulate in the Northern Hemisphere this winter still remains really undefined. If you remember Europe didn't have very many of the 156K viruses at all. We had them come towards the end of our H1N1 season is when they really came into the U.S. and started to increase. And that's when they saw more 156K viruses as well in the Southern Hemisphere at the start of

their season, like particularly in Australia and the Philippines -- you know, surrounding areas that the VIDRL gets specimens from.

So maybe I'm not answering your question. But the other part of it is if you remember the hemagglutinin molecule structure that I went through, remember that crystal structure with all the little dots that are color coded on it, those -- we're making the 156K and the 187 seem so different from each other. But really, we're talking about they're different -- in the antigenic sites, they differ from each other by two amino acids, right? One of them have these 156K and 161 change, and one of them has the 187, 189 change, right? But they all have the same backbone change as of the 185, the 183 and those weren't -- all those backbone changes that are part of the 5A supergroup weren't in our vaccine previously and are now.

So we don't have a good idea of how well the 187 selection in humans will do against these 156 viruses. And we won't until we have human sera, which

we'll get in December/January this year from people getting vaccinated now, to look at how well the human sera generated against that current vaccine works against the 156 viruses.

I can also tell you in other animal models, they don't see the difference -- the stark difference -- between the 156 and the 187 viruses that ferrets do. For example, we're using mice more now with these because of this issue with the ferrets focusing solely on the site-Sa. And what we see with our preliminary data there is that by updating the vaccine to 183 and now to the 187 group, it better covers the 156 viruses. So I'm kind of hoping that human immune response is a little more like the mouse immune response than the ferret immune response.

DR. EL SAHLY: That's great. So we have some data to discuss in March already.

DR. WENTWORTH: Yeah. We will. They'll be a very -- it's not an experiment, but it's a very -- I said, you know, I --

DR. EL SAHLY: Yeah, it's not --

DR. WENTWORTH: -- I think my point is we've moved the vaccine up to the most recent antigenically advanced groups that share more amino acids together than they diverge from. Out of those 560 amino acids, they're very closely related.

DR. EL SAHLY: Okay.

DR. WENTWORTH: And, of course, there's more than receptor binding neutralizing antibodies to our immune response to flu.

DR. EL SAHLY: Okay. All right. Thank you. I think the last question is from Mr. Toubman. Sheli (phonetic), please unmute yourself and ask the final question. Sheli, you're still on mute it looks like.

MR. TOUBMAN: Can you hear me now?

DR. EL SAHLY: Yes, we can.

MR. TOUBMAN: Thank you. I see I'm not moving but -- in terms of the impact of the pandemic, I have a question at the beginning was about what was the circulation obviously and the impact of that. A

related question is about travel. I guess, you know, people do their absolute best, obviously, in making the educated guess about where it's going to be a year from now. But this is an extremely different situation where travel -- international travel -- particularly, has vastly reduced. So my question is what impact does that have in the guesstimating, given the fact that we can expect far less international travel probably up until next summer?

DR. WENTWORTH: Yeah, I mean, my short answer is I don't know. I think what you can imagine, and what people think about, is the reductions in travel reduce spread of the more novel variance. And they create more of a geographic pocket where different viruses might evolve like four different populations. And so you have less mixing of the different clades than we normally see.

You can think of a place like New York City and how many different viruses, from globally, show up in New York City in the course of three or four months.

And that's going to be reduced in part because of these reductions in travel.

But, I think, what we're thinking is that the most fit clades will still be moving around to a certain extent, but there could be -- you know, how I showed these maps where we show the geographic distribution, and how they're already are pockets where some clades seem to be doing -- you know, they're the most predominant clade and other clades really aren't there. And that could get worse is my short answer there. Because if there's much less travel, that group of viruses may be just fine in that population and it isn't displaced by a slightly more fit virus from another location. So I think it may become less homogeneous than it already isn't very homogeneous.

MR. TOUBMAN: Thank you.

DR. EL SAHLY: Okay. Okay. So that concludes this session. Thank you so much, Dr. Wentworth, for going through these slides and explaining to us all these details regarding the antigenic relatedness and

the circulation trajectory of these viruses.

We will now take a break for lunch. The plan is to reconvene at 1:30 p.m. Eastern time, so that gives us 40 minutes of break. Thank you all.

MS. HAYES: And, if everyone could please stay connected with your phone and also in the meeting, that'll just make it easier to get started so we don't have to reaccept anybody back into the room. Thank you.

[LUNCH BREAK]

MR. KAWCYNSKI: Thank you and welcome back from our break. We are going to begin started with the after-lunch portion, so I'm going to hand this back to my colleagues. Kathleen, do you want to take it away? It'll kick on.

MS. HAYES: Yeah. Hi, everybody. Welcome back. We are going to move into the next portion of our meeting. Dr. El Sahly, did you want to make any statements about the OPH session?

OPEN PUBLIC HEARING

DR. EL SAHLY: Hi. Can you hear me?

DR. WENTWORTH: Yes.

MS. HAYES: Yes, I can.

DR. EL SAHLY: Okay. So it seems that no one has registered for the open public hearing session, so we will be moving to the next portion of our meeting, which is the discussion and the voting and the recommendation.

COMMITTEE DISCUSSION, VOTING AND RECOMMENDATIONS

DR. EL SAHLY: I will be giving the opportunity to all of our members to comment on the presentation today and final thoughts on the recommendations prior to voting. As I go around and state your name, please unmute yourself and let us know if you have a comment; or if none, then we'll just move to next committee member. Starting off with Dr.

Beckham. Dr. Beckham, did you have any comments or final thoughts on the presentation today?

DR. BECKHAM: Hi. No. Excellent presentation. Thank you very much for that. No additional thoughts or questions.

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

DR. CHATTERJEE: Thank you, Dr. El Sahly and Dr. Wentworth, for your presentation. I share the concern about having so few samples to make the decision about the choice of strains, but, other than that, I have no other comments.

DR. EL SAHLY: Okay. Thank you. Dr. Cohn.

CAPT. COHN: Thank you, Dr. Wentworth, for a great presentation. I concur with Dr. Chatterjee. I am also concerned about the low number of strains but believe that you guys have done an amazing job with the data that you do have and concur with the proposed strains.

DR. EL SAHLY: Thanks, Dr. Cohn. Dr. Gans.

DR. GANS: Hi. Yes. Thank you. My only

comment -- I mean, I already told Dr. Wentworth I thought it was an excellent presentation. My only comments are, it would be nice to know about the data about persistence of immunity just because, to your point, Hana, I mean, we had for a predominated to target the 187, now we're going to change to the 156.

But, if people are vaccinated previously, they should have good responses. But it would be nice to know just some of the data around that we assume from past epidemiologic and from other studies that there is persistence not widely immunized every year. But that would be nice to document.

The other part of this that I think is missing. I mean, we have discussions and we obviously can come to this ourselves, but it would be nice to associate the specific recommendations with what exactly we are targeting in terms of the 187, versus the 156, versus whatever else that's in there. Those are my only comments. I completely agree with the recommendation.

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

DR. JANES: Thank you. I really appreciated the discussion about the number of strains that are available, and the issue with the representativeness of them and challenges with determining what the denominator is. I wholeheartedly concur with Dr. Gans' suggestion to characterize the durability of the immune responses to help us make decisions about changes to the strain from season to season. I concur with the recommendation then. I really appreciated the discussion and presentation. Thank you.

DR. EL SAHLY: Thanks, Dr. Janes. Dr. Kurilla.

DR. KURILLA: No comments.

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

DR. LEVINE: I would just add my thanks and kudos to the great presentation that David Wentworth gave. I have nothing to add to the cogent comments that have already been made.

DR. EL SAHLY: Okay. Thank you. Dr. Meissner.

DR. MEISSNER: Thank you. I guess, the more I listen to the experts talk about influenza, the more confusing this whole topic. It is so hard to anticipate what's going to happen this year with the influenza season. On one hand, it may be mild as we have seen so far, and then there are other descriptions of people who have co-infections with influenza B and SARS-CoV-2 may have more severe disease than with either one alone.

It's just a fascinating issue, and there's not much in infectious diseases that's more interesting. But I also want to thank David Wentworth for presenting just an enormous amount of data. And I think I have nothing more to add. Thank you.

DR. EL SAHLY: Thanks, Dr. Meissner. Dr. Offit.

DR. OFFIT: Yes, I just want to thank Dr. Wentworth for making it clear to me why it is that the

head of the influenza lab at Wistar when I was younger once said to me, "If you want a research career that lasts for the rest of your life, study influenza."

DR. EL SAHLY: Okay. Did you listen to his advice?

DR. OFFIT: No.

DR. EL SAHLY: All right. Dr. Pergam. Thank you, Dr. Offit.

DR. PERGAM: Yeah. I don't think there's much to add other than thanks, Dr. Wentworth, for that amazing review. It's always amazing. It was interesting how much one learns when listening to these talks. I think most of the comments that I would have made have been covered by others. But thanks again for that great discussion.

DR. EL SAHLY: Thanks. Dr. Shane. You may be on mute, Dr. Shane.

MS. HAYES: I think she may be trying to reconnect.

DR. EL SAHLY: Okay. We'll circle back to Dr.

Shane. Dr. Spearman.

DR. SPEARMAN: I have no further comments. Thank you very much for the presentation. It was excellent.

DR. EL SAHLY: Thanks. Dr. Swamy.

DR. SWAMY: Thank you. No further comments than those have been made by the group so far.

DR. EL SAHLY: Thanks, Dr. Swamy. Mr. Toubman.

MR. TOUBMAN: I would just, yeah, thanks, Dr. Wentworth, for an excellent presentation. It also reinforces the value of the international system, WHO's global monitoring. I just don't see how we could possibly get a handle on this without the oversight of that body and, obviously, Dr. Wentworth's an important component in that. So just a great thank you for the presentation and for the existence of that system, and I don't have any reason to disagree with the recommendations. Thank you.

DR. EL SAHLY: Thank you. Dr. Annunziato.

You may be on mute, Dr. Annunziato.

DR. ANNUNZIATO: Thank you. I'm sorry. I had some problem with the microphone. So, yes, I also just want to add my thanks to the presenters and to note that the vaccine manufacturers greatly appreciate the systematic surveillance and the careful scientific investigations that guide these semiannual selections of the influenza strains.

We heard some amazing and unprecedented dynamics this morning about these strains, and it just points out how really important this work is.

DR. EL SAHLY: All right. Thank you, Dr. Annunziato. Final comments from Dr. Wentworth before going to the CBER representatives.

DR. WENTWORTH: I really don't have any additional comments. I really appreciate your comments on the presentation. It's certainly a team effort on our part here at the CDC, and as was mentioned, the WHO and GISRS labs really play key rolls there. So some of the data used is directly from them and not even from

the CDC. So thanks very much.

DR. EL SAHLY: Thank you. Dr. Weir.

DR. WEIR: I don't have anything to add. I appreciate all of the comments.

DR. EL SAHLY: Okay. Dr. Krause? You may be on mute, Dr. Cross.

MS. HAYES: I don't think Dr. Krause was on today.

DR. EL SAHLY: Oh. Okay. I have his name for discussion. Dr. Gruber.

DR. GRUBER: Yeah. Hi. This is Marion. I don't have anything to add. I just wanted to also thank David Wentworth for an excellent presentation of the data and thank the committee for their comments, so thank you so much.

DR. EL SAHLY: Thank you, Dr. Gruber. I'm going to circle back and see if Dr. Shane managed to reconnect.

DR. SHANE: Yes, I did. Apologies. Thank you very much for the lovely presentation of this very

educational, and I don't have any additional comments. Thank you.

DR. EL SAHLY: Thank you, Dr. Shane. So to sum it up, I also want to echo how amazed we are at the collaborative effort that yields this breadth and depth of data on the influenza surveillance and the trajectory of the epidemic year after year.

I have nothing else to add or a reason to question the recommendation, except that the following season is going to be a very interesting season given all the vital and social dynamic at play. With that, we will move to the voting unless Kathleen tells me I have something else to do. Are we good with voting?

MS. HAYES: I think we can move to voting.

DR. EL SAHLY: Okay.

MS. HAYES: I'm going to just check in on one other thing to make sure that our webcast is set and that people are able to hear fine. Just one moment.

DR. EL SAHLY: Okay.

MS. HAYES: Okay. So it looks like we are

good to go. So we can proceed with the voting. You will see each question that needs to be voted upon on this slide, and Dr. El Sahly will read each question for the record. Then afterwards all members will cast their vote by selecting one of the voting options, which include yes, no, or abstain. And then, once all of the votes have been placed, I will broadcast the results and read the individual votes aloud for the record.

DR. EL SAHLY: Okay. Do you want to post the questions?

MS. HAYES: Yes. If we can move into the first voting slide. Okay. Here's our voting question.

DR. EL SAHLY: Okay. For the composition of egg-based trivalent 2021 Southern Hemisphere formulations of influenza vaccines, does the committee recommend: A) Inclusion of an A/Victoria/2570/2019(H1N1)pandemic09-like virus; B) Inclusion of an A/Hong Kong/2671/2019(H3N2)-like virus; C) Inclusion of a B/Washington/02/2019-like virus

(B/Victoria lineage)? The options are yes, no or abstain. Please vote.

DR. KURILLA: Hana, I'm only getting the option to vote on the item 2. Is that correct?

DR. EL SAHLY: Well, I have the same. It says Voting Question Number 1, and then it says vote item 2. Let me check verification for all. I think we're voting on Question 1, so it should be okay.

DR. KURILLA: Okay. Thank you.

DR. MEISSNER: Oh, it looks like it just came back again to us.

DR. EL SAHLY: Kathleen, should we ask everyone to vote again, or did it go through?

MS. HAYES: Yes, if you could just, please, input your votes.

DR. EL SAHLY: Okay. Please vote again, and we are voting on Question Number 1 as displayed.

MS. HAYES: Okay. So it looks like all of the votes are in, and we have a unanimous yes among all the members, so this vote passes. I will now read just the

individual member votes for the record. Dr. Pergam, yes; Dr. Gans, yes; Dr. Meissner, yes; Mr. Toubman, yes; Dr. Shane, yes; Dr. Beckham, yes; Dr. El Sahly, yes; Dr. Offit, yes; Dr. Swamy, yes; Dr. Levine, yes; Dr. Cohn, yes; Dr. Spearman, yes; Dr. Janes, yes; Dr. Chatterjee, yes.

DR. EL SAHLY: Okay.

MS. HAYES: Dr. Meissner, yes. And that should conclude.

DR. EL SAHLY: All right.

MS. HAYES: So we can now move on to the second voting question.

DR. EL SAHLY: Okay. Question Number 2. For quadrivalent 2021 Southern Hemisphere formulation of influenza vaccines, does the committee recommend the inclusion of a B/Phuket/3073/2013-like virus (B/Yamagata lineage) as the 2nd influenza B strain in the vaccine? Options again, yes, no or abstain. Please vote.

MS. HAYES: Okay. It looks like all the votes

are in, and similar to the previous question we have a unanimous yes among all the members, so this vote passes. I will read the individual member votes for the record. Dr. Pergam, yes; Dr. Gans, yes; Dr. Meissner, yes; Mr. Toubman, yes; Dr. Shane, yes; Dr. Beckham, yes; Dr. El Sahly, yes; Dr. Offit, yes; Dr. Swamy, yes; Dr. Levine, yes; Dr. Cohn, yes.

DR. EL SAHLY: Okay.

MS. HAYES: Sorry. Just one moment. Dr. Janes, yes; Dr. Chatterjee, yes; Dr. Kurilla, yes; Dr. Spearman, yes. And this concludes the vote.

DR. EL SAHLY: Okay. Well, with that I want to thank everyone for taking the time to meet today and review the data and provide their comments and their votes on the topic of discussion, which is the strain selection for the Southern Hemisphere influenza vaccine strains. Hopefully, we will reconvene soon and probably in another virtual setting. Bye, everyone.

[MEETING ADJOURNED]