FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
157th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION - TOPIC II

FDA White Oak Campus
Great Room, Salon B & C
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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

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DR. EL SAHLY: Moving on to Topic II. Topic II today will be the strain selection for the 2020 Southern Hemisphere influenza season.

CPT. HUNTER-THOMAS: Dr. El Sahly, hold on one moment. I'm sorry. We would like to open up the meeting again for all to attend.

DR. EL SAHLY: Okay. Let me know when ready.

CPT. HUNTER-THOMAS: Yes. Thanks.

(Pause.)

CPT. HUNTER-THOMAS: Hana, we're just going to wait a few more minutes to make sure the WebEx is back up and also that our CDC speaker has rejoined and the industry rep and so on. Okay? And we'll do a quick roll call before we start with Topic II. Thanks.

(Pause.)

DR. EL SAHLY: Hello?

CPT. HUNTER-THOMAS: Hello.

DR. EL SAHLY: Serina, are we ready?

CPT. HUNTER-THOMAS: Let me get two more minutes and then we'll do a roll call, Hana.

DR. EL SAHLY: Okay. Very good.

(Pause.)

CPT. HUNTER-THOMAS: Okay. I just want to start with the roll call now. Dr. El Sahly, would you like to start with the roll call, or should I?

DR. EL SAHLY: You can go ahead. Thank you.

CPT. HUNTER-THOMAS: Okay. So starting with Dr. El Sahly, of course. And then Dr. Gans?

DR. GANS: Yes, I'm here.

CPT. HUNTER-THOMAS: Okay. Dr. Janes? Dr. Holly Janes? Okay. Dr. Michael Kurilla?

DR. KURILLA: Here.

CPT. HUNTER-THOMAS: Thank you. Dr. Cody Meissner?

DR. MEISSNER: Here.

CPT. HUNTER-THOMAS: Thank you. Dr. Paul Spearman?

DR. SPEARMAN: Here.

CPT. HUNTER-THOMAS: Thank you. Dr. Geeta Swamy?

DR. SWAMY: Here.

CPT. HUNTER-THOMAS: Thank you. Mr. Sheldon

Toubman?

MR. TOUBMAN: I'm here.

CPT. HUNTER-THOMAS: Thank you. Dr. Melinda Wharton?

DR. WHARTON: Here.

CPT. HUNTER-THOMAS: Thank you. Circling back to Dr. Holly Janes?

DR. JANES: Yes, I'm here. Sorry.

CPT. HUNTER-THOMAS: That's okay. Thank you. And checking for Dr. Tammy Beckham, if you've rejoined us? How about Dr. Lisa Bollinger? And Dr. David Wentworth? So Hana, we'll need a few more minutes for them to join because they had to drop off for the closed session. They have been notified to join us back again.

DR. EL SAHLY: Okay. So we're waiting on Dr. Bollinger and Tammy Beckham?

CPT. HUNTER-THOMAS: Bollinger, Beckham, and Wentworth.

DR. EL SAHLY: Okay. All right.

CPT. HUNTER-THOMAS: Okay. Thanks.

DR. EL SAHLY: Thank you.

(Pause.)

CPT. HUNTER-THOMAS: Okay. Checking in again for Dr. Tammy Beckham? Dr. Steven Pergam? Dr. Lisa Bollinger?

DR. BOLLINGER: I'm here.

CPT. HUNTER-THOMAS: And how about Dr. Wentworth? Okay. We're making progress. Holding for Dr. Wentworth and Dr. Beckham. We'll give a few more minutes. Thank you.

(Pause.)

CPT. HUNTER-THOMAS: Dr. Beckham?

DR. BECKHAM: Yes.

CPT. HUNTER-THOMAS: Dr. Wentworth? Dr. Pergam? Okay. We'll wait a few more minutes for Dr. Wentworth.

(Pause.)

CPT. HUNTER-THOMAS: Dr. David Wentworth, are you with us now?

DR. WENTWORTH: Yup. I just joined. Apologies if I was holding things up.

CPT. HUNTER-THOMAS: Oh, that's fine. We're still ahead a little bit. Thank you.

DR. WENTWORTH: Excellent. Great.

CPT. HUNTER-THOMAS: So we will go ahead and get started, Dr. El Sahly.

TOPIC II: STRAIN SELECTION FOR THE 2020 SOUTHERN HEMISPHERE INFLUENZA SEASON

DR. EL SAHLY: All right. Thank you all again for joining the second portion of today's meaning, namely the strain selection for the 2020 Southern Hemisphere influenza season. Captain Serina Hunter-Thomas will read some housekeeping items now, including the conflict of interest statement.

ADMIN ANNOUNCEMENTS, COI STATEMENT

CPT. HUNTER-THOMAS: Thank you, Dr. El Sahly. As far as housekeeping, just a reminder for all of the committee members and speakers to mute your phones while there are presentations and also to mute the

microphone that is within the Adobe Connect environment. And I'll proceed with the COI statement.

The Food and Drug Administration is convening today, October 9, 2019, for the 157th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as the Chair of the meeting for Topic II. Today, for Topic II, 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 2019/2020 Southern Hemisphere influenza season. This topic is determined to be a particular matter involving specific parties.

Related to the discussions at this meeting, all members 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. Excuse me. These interests may include

investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment. FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interests laws.

Under 18 U.S. Code 208, Congress has authorized the FDA to grant waivers to Special Government Employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Lisa Bollinger is currently serving as the acting industry representative to this committee. Dr. Bollinger is employed by Amgen.

Industry representatives act on behalf of all related industry and bring general industry perspective

to the committee. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee; hence, industry representatives are not screened and do not participate in the closed sessions and do not have voting privileges. Mr. Sheldon Toubman is serving as the consumer representative for this committee.

Consumer representatives are special appointed government employees -- excuse me -- appointed Special Government Employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee and, hence, do have voting privileges. And they do participate in the closed sessions if they are held.

Dr. David Wentworth is employed by the Centers for Disease Control and Prevention and serves as the Chief of the Virology Surveillance and Diagnosis branch in the Influenza Division. He is an internationally known expert in influenza virus epidemiology, worldwide influenza disease burden, and influenza virus vaccines. Dr. Wentworth is a regular government employee and

serves as a speaker for this meeting under Topic II. He is also serving as a temporary non-voting member for Topic II.

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 with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm who's product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products, and, if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest the participants need to inform the

DFO and exclude themselves from such involvement. And their exclusion will be noted for the record. This conflict of interest statement will be available for public viewing at the registration table. This concludes my reading of the conflict of interest statement for the public record. And at this time, I would like to hand the meeting back over to Dr. El Sahly. Thank you.

DR. EL SAHLY: Thank you, Serina. Dr. Jerry Weir, who's the Director of the Division of Viral Products Office of Vaccines Research and Review, will now do an introduction and presentation of questions for the committee.

INTRODUCTION AND PRESENTATION OF QUESTIONS

DR. WEIR: Thank you and good morning again to everyone. I'm going to provide just a very brief introduction to the topic of this portion of the advisory committee meeting. The purpose of today's VRBPAC committee discussion is to make recommendations

for the strains of influenza A, H1N1, and H3N2 and B viruses to be included in the 2020 Southern Hemisphere formulation of influenza vaccines, which are licensed in the United States.

The next slide shows and describes a little bit of the background. Many of you on the committee have been through this process a few times, but this just serves to remind you, as well as anybody that hasn't gone through this process before. The World Health Organization makes recommendations for the virus strains to be included in the influenza vaccines two times a year. The recommendations made for the Northern Hemisphere are made in February or March for the next winter Northern Hemisphere season. And they make recommendations for the Southern Hemisphere usually in September of each year for the next Southern Hemisphere influenza seasons, which is our summertime: June, July, August.

But in addition to the World Health Organization recommendations, it's national regulatory authorities must approve the composition and

formulation of vaccines in each country. For example, the VRBPAC provides the recommendation for U.S. licensed vaccines in February or March for vaccines to be used in the Northern Hemisphere influenza seasons. And the FDA CBER approves license supplements for each U.S. manufacturer to incorporate and update its strain recommendation. This usually occurs in June or July for the following Northern Hemisphere seasons.

But in 2016, one U.S. vaccine manufacturer was approved to produce a Southern Hemisphere formulation of their influenza vaccine. This was an egg-based vaccine. We anticipate that other manufacturers may also ask us to approve Southern Hemisphere formulations; and so it's important that strain recommendations and supplement approval for any Southern Hemisphere formulation follow the same Northern Hemisphere process that we use.

So today, this discussion today is somewhat abbreviated compared to the one that we do in February or March for the Northern Hemisphere, but you'll hear examples of the same type of data.

Most of this is what is a short version of what was discussed and presented at the World Health Organization meeting a couple of weeks ago. You'll hear from CDC about the epidemiology of currently circulating strains, surveillance data from the U.S. as well as from around the world. You'll see data presented on the antigenic relationships among contemporary viruses and candidate vaccine viruses.

This will include hemagglutination inhibition and virus neutralization data, also hemagglutination inhibition and virus neutralization tests on using panels of sera from humans receiving recent inactivated influenza vaccines. Some data will probably include antigenic cartography as well as phylogenic analysis of HA and NA genes.

The next couple of slides I'm going to recap what's gone on in the past few recommendations. Starting about a year ago, the previous recommendation for the Southern Hemisphere formulation for 2019 -- in other words the season that just sort of is ending now or has ended in the Southern Hemisphere.

About this time last year, on September 27, the WHO made its recommendation for the Southern Hemisphere formulation. And that was that vaccines would include an A/Michigan/45/2015(H1N1) pandemic 09-like virus, an A/Switzerland/8060/2017(H3N2)-like virus, a B/Colorado06/2017-like virus from the B/Victoria lineage. And the WHO also recommended that quadrivalent vaccines that would contain two influenza B viruses contain the above three viruses plus a B/Phuket/3073/2013-like virus from the B/Yamagata lineage. The VRBPAC recommendation for U.S. manufacturers' Southern Hemisphere formulation was the same as that of WHO, and this occurred on October 3, 2018.

Since that time, we had, of course, a Northern Hemisphere vaccine recommendation. For those of you who were part of this may remember the WHO recommendation occurred in two phases on February 21 and March 21. This was because of the delayed recommendation for the H3N2 strain this past winter.

But anyway, the final recommendation was that

viruses for the Northern Hemisphere trivalent vaccine contained an A/Brisbane/02/2018(H1N1) pandemic09-like virus, an A/Kansas/14/2017(H3N2)-like virus, and a B/Colorado/06/2017-like virus from the B/Victoria lineage. In addition, the recommendation for quadrivalent vaccines was to include a B/Phuket/3073/2013-like virus from the B/Yamagata lineage.

Our VRBPAC recommendations also followed this last year -- the WHO recommendations. And we made these in two different VRBPAC meetings, one on March 6 and one on March 22.

Recently, this year, the WHO recommendation for the upcoming 2020 Southern Hemisphere formulation was announced on September 27, 2019. This WHO recommendation was an egg-based trivalent vaccines for use in the 2020 Southern Hemisphere contain an A/Brisbane/02/2018(H1N1) pandemic09-like virus, a A/South Australia/34/2019(H3N2)-like virus, a B/Washington/02/2019-like virus from the B/Victoria lineage and additionally for quadrivalent vaccines, the

WHO recommended these three viruses and B/Phuket/3073/2013-like virus from the B/Yamagata lineage.

Today, the committee will discuss which influenza strains should be recommended for the antigenic composition of the Southern Hemisphere formulation of influenza virus vaccine produced by licensed U.S. manufacturers.

And the questions, we will have two. The first question will be for the composition of trivalent 2020 Southern Hemisphere formulation of influenza vaccines. Does the committee recommend an inclusion of an A/Brisbane/02/2018(H1N1) pandemic09-like virus, an A/Australia/34/2019(H3N2)-like virus, and a B/Washington/02/2019-like virus from the B/Victoria lineage?

And then a second question that the committee will be asked to vote on will be for quadrivalent 2020 Southern Hemisphere formulations. Does the committee recommend the inclusion of a B/Phuket/3073/2013-like virus from the B/Yamagata lineage as a second strain?

Thank you.

WORLD SURVEILLANCE

DR. EL SAHLY: Dr. Weir presented us with the charge today. Thank you, Dr. Weir. Next up is Dr. David Wentworth, Chief of the Virology Surveillance and Diagnosis Branch, Influenza Division, at the CDC in prevention, who will do a world surveillance review of the circulating influenza strain. Dr. Wentworth?

DR. WENTWORTH: Thank you. So, we can move off of that title slide to the second slide, which is entitled Global Influenza Surveillance and Response System, which is the GISRS. So, I think many of you are aware of this, but I will walk through it rather briefly -- that there's continuous surveillance conducted by GISRS globally. This included work from WHO collaborating centers, such as the one at the CDC, national influenza centers around the world, WHO essential regulatory laboratories, which Dr. Weir just discussed, and WHO H5 reference laboratories that are involved in the zoonotic surveillance, which I will not

go into today.

So, the WHO consultation was held from the 23rd to the 26th of September where we reviewed and analyzed all the data and came to a conclusion. This was chaired by Dr. Kanta Subbarao of the WHOCC VIDRL in Australia. So, she is the director there, along with the nine advisors: Drs. Hasegawa, McCauley, Wang, myself, Dr. Webby, Zhiping Ye, Dr. Yi, Dr. Bharadwaj, and Dr. Engelhardt. And then we had 21 observers from various NICs H5 reference laboratories, other members of the CCs and ERLs, along with the academic and veterinary sector from OFFLU and other government agencies.

So, the next slide, on slide 3, shows the global circulation pattern of influenza viruses. This is taken from a WHO GISRS site, so you can see really the global level for the Southern Hemisphere. Along the bottom axis, you can see the weeks of the year, starting with the 2018 weeks and then shifting into 2019. And the color coding -- uh-oh. Hopefully everyone can see that. Can you still hear me okay?

DR. MEISSNER: Can hear you, can't see anything. Nothing is being shared is the message we're getting.

DR. WENTWORTH: Yeah. That's what happened to mine, as well.

CPT. HUNTER-THOMAS: Okay. Standby. We'll check on this end.

DR. MEISSNER: Well, the slides are available separately.

DR. GANS: I have the PDF that was sent out so can follow along if others have that as well.

DR. SPEARMAN: Yeah. I've got mine, too. This is Paul Spearman.

CPT. HUNTER-THOMAS: Okay. We're going to hold for a moment because we would like the public -- for the benefit of the public to follow along as well.

DR. MEISSNER: While we're waiting -- this is Cody Meissner. May I ask a question of Dr. Weir, or do you want to wait?

CPT. HUNTER-THOMAS: Sure. Go ahead.

DR. MEISSNER: I just wondered, Dr. Weir, if

you could clarify why the selection of strains for the Southern Hemisphere comes under FDA purview. I think you mentioned there's one pharmaceutical company that makes the Southern Hemisphere strain, but it's not used, I don't think, in part of the United States. So why does that come under FDA regulation?

DR. WEIR: Okay. So just briefly, it comes under our purview because they submit a supplement to their license to produce this under the U.S. license. How they distribute it and what they use it for, of course, is a company decision. But because they come to the Agency and submit it to us to supplement their license, we must act on it.

It also turns out that there is something sort of important that the package inserts for all of these vaccines state -- and this occurs for this manufacturer that produces a Southern Hemisphere formulation -- to keep all of the recommendations consistent. It actually states in their insert that the recommendations follow public health service recommendations. So again, this is just our

responsibility to make sure that, if they're going to produce it under a U.S. license, that we approve it.

DR. MEISSNER: Thank you. That's interesting. And I notice some of your slides -- it looks like we still have a minute -- say egg-based vaccine. Does that mean that the cloned vaccine, for example, is not used in the Southern Hemisphere?

DR. WEIR: Actually, that's sort -- now that you mentioned it, I noticed it when I flashed up the slides. As you might guess, I update these slides every time we do this. And in one of our recent advisory committee meetings, there was actually a different recommendation for a cell-based vaccine versus an egg vaccine. And so, the language I used in these slides I specified egg-based vaccines, which is appropriate for the manufacturer in question. But probably, I could have just left it out.

As you will see when David Wentworth finishes his presentation, there was only one recommendation in this WHO committee recommendation for a vaccine composition. There was nothing different for cell-

based vaccines versus egg-based vaccines. But yes, the bottom line is that the manufacturers that produce it for Southern Hemisphere are egg-based vaccines at the present time.

DR. MEISSNER: Thank you.

CPT. HUNTER-THOMAS: Just checking in. Can everyone see the webcast now?

DR. SPEARMAN: Yes.

DR. GANS: Yes, I can.

CPT. HUNTER THOMAS: Okay. We're back in business. Dr. Wentworth, apologies. You can proceed.

DR. WENTWORTH: Thank you very much. So as I was saying, the weeks of the year are on the bottom, and the 2018 versus 2019 is shown further down. And you can focus in on the 2019 season. You can see that, as a general overall peak to the season, we really started to ramp up about week 19 and ended week 35 and 36. So you can also see this is a stacked bar graph. And the more orange colors are the B viruses. And these are broken out.

You can see the B/Victoria lineage is the kind

of brighter orange and the lighter color is the Yamagata lineage. And what you can appreciate there just with the B viruses is there was more Victoria circulating globally than Yamagata. And then the un-subtyped, or lineage not determined, group is the dark burnt orange color.

If we go to the light blues or the blue series, we have not subtyped, which is the dark blue. And then A(H3) virus is the more aqua, and the sky or lighter blue are the H1 viruses. And hopefully what you can appreciate there is they circulated in about equal numbers globally. There is difference geographically, obviously. And I'll go into some of that a little bit later. So, we've moved to the next slide. This slide --

DR. KURILLA: David, one question related to that last slide. Given the ubiquitous-ness of sequencing capabilities, why is there such a high percentage of un-subtyped?

DR. WENTWORTH: Yeah. That's related to the national influenza centers. So, all this data is

coming in through some of the GISRS network. And all of the viruses are genomically characterized in that way. There's both typing, which is easily done by real time PCR, as well as subtype and lineage detection, which is also done by sequential real time PCR.

So most of this data comes from PCR diagnostic technologies. And a lot of the NICs, while it may be available, don't bother doing the subtyping or lineage detection on some subsets of their viruses. We can glean from the percentages of the ones that are done what those that aren't characterized would be. Hopefully, that addresses that question.

DR. KURILLA: Thank you.

DR. WENTWORTH: So, you can see this is in the thousands every week, globally. So, if we move to the next slide, this is slide 4, the numbers of specimens processed by GISRS. You can look at the red line. You can see that that's the 2019 trend, which is following previous seasons' trends, not too much to dwell upon here.

Slide 5, this is going to show you the

percentage of influenza viruses by subtype and lineage. So now this is the grand total of that, so it's kind of like collapsing that previous slide that the question was on.

And again, you can see there's a lot of A that's not subtyped, 50 percent. But what you can also see is that the ones that are done, the H1N1 represented 19 percent and A/H3N2 viruses represented 18 percent. So, they were about equal proportions. Again, B not determined is this burnt orange color. And this you can more easily appreciate the difference between the Victoria and the Yamagata, how many were circulating globally.

If we move to the next slide, this is slide 6, influenza virus as sequenced and available via GISAID. So, this gets to the sequencing question. A lot of the sequencing is done still primarily by the collaborating centers. But some of the national influenza centers are doing more and more now.

Anyway, so this illustrates how many thousands of sequences per each of the subtypes and lineages were

deposited. And it does show a little bit of the proportionality of the viruses that are available for the analysis.

If we move to the next slide, this is illustrating the antigenic characterization during the past three Southern Hemisphere reporting periods, 2017 in the blue bars, 2018 in the red bars and 2019 in the green bars. And what you can see is there's thousands of viruses in the H1, H3, about 2,000 in each category, and B that were antigenically characterized by all the collaborating centers through this period. Now I'm going to move to slide 8. This is going to move into the H1N1 PDM09 virology section, along with a bit of epidemiology. So, if we move to slide 9, this is illustrating the activity globally.

So widespread outbreaks are the dark red colors. And you can see the continents and countries where widespread outbreaks occurred along with regional outbreaks. So, we saw quite a bit of H1N1 in the United States, parts of South America and Russia and Asia, for the most part; and more sporadic activity in

other countries and regions were reported.

If we move to the next slide, this is now focusing on the number of H1N1 viruses detected by the GISRS network. You can see that early in the week of the year -- so the red line is 2019. The green line is 2016 where we had a pretty good H1 season. Whereas 2017, there was not too many H1s around, and 2018 there was a moderate amount. So, you can see they peaked early this year and then fell off by about week 14 or so and have continued that way in the inter-seasonal levels until present.

Go to the next slide. This is now getting into some of the genetic characteristics of the hemagglutinin gene. I know it's a bit small, but we have to do it that way since this represents about 4,000 sequences on this tree that are collected and available since February 2019. I'm going to take a bit of time to walk you through the tree because I'll be using some of these names later in the presentation, and hopefully they'll stick.

So, Dr. Weir mentioned the previous Southern

Hemisphere vaccine. That's at the very bottom of this tree. It's called A/Michigan/45/2015, and I have a red arrow pointing to that because it's way down at the bottom. And then, virtually the entire tree is represented by this blue bar. This is clade 6B1.A, and it is really characterized by three major substitutions which are near the base of this tree. They're S74R, S164T, and Q295B. So, they're down there at the bottom of that tree.

But then the entire tree is made up of these 6B1A viruses, and they can be divided into various subclades, which you can see the other bar is trying to represent those. And the nomenclature for these is called 183P- a number. So, the very bottom there is 183P-7. It's that purple bar. Then we have 183P-2, P-1, and the virus representing the P-2 group is this Maine virus, which is a unique virus that I'll discuss in a bit, the Brisbane/02-like virus, which was recommended for the Northern Hemisphere vaccine, and the Idaho/7 virus, which is the cell vaccine candidate.

So, Brisbane/02 is egg vaccines. Idaho/7 is a

cell vaccine candidate, and they're both there in a 183P group. And we have viruses representing Iowa/12, which is a P-5 group; Iowa/33 also in that group; and then way at the top of the tree in this 183P-5A group, which is expanded the most extensively in the recent months, is the Wisconsin/505 serology antigen virus. Okay. I'm going to move to slide 12 now.

This illustrates the HA molecule, the monomer which normally forms a trimer, but it's easier to see some of these changes on the monomer. And on the left-hand side, you can see the major change that I just described, and we've described in previous VRBPAC, is this 183P, which, as you saw from the phylogenetic tree has arisen multiple times through parallel evolution in the viruses circulating in people. And hence, the clade namings all have this 183P, but they might be arising from a different progenitor virus on the tree.

Then, if we turn that molecule 180 degrees, you can see other changes that are up in the head of the protein that could affect antigenicity. And they are S164T and S74R. So, this is the molecule Idaho/7,

which is a cell candidate vaccine virus, compared to Michigan, the previous vaccine virus. So those are highlighting the major changes. The orange dots on the molecule, or specific amino acid residues on the molecule, really represent areas where glycans are predicted to exist.

If we move to the next slide, this is showing you the reactivity patterns seen by the collaborating centers in hemagglutination inhibition assays with H1N1 viruses that are circulating. And they're ranked by -- they're considered antigenically like Michigan/45 or antigenically low compared to Michigan/45 antisera by the WHOCCs. And this is ferret antisera raised against Michigan/45. So, on the left-hand side, we're comparing the cell -- antisera raised against the cell propagated cultivar of Michigan/45. And that's under the green bar. And under the blue bar, we're comparing against the egg cultivar.

So, you can see that the CDC, 95 percent of them are considered antigenically like, and we saw about five percent that were considered low. So, they

have eightfold or greater reduction in homologous hemagglutination inhibition titers. And similar patterns are seen by all the other collaborating centers, CNIC, NIID, which is in Japan, in VIDRL in Australia. On the righthand side, you can see the numbers for all the CCs against the egg viruses, and you can see pretty good similarities between the cell and the egg in this particular case with the H1N1 viruses. And at the very bottom, you can see the Crick data where they used primarily the egg for comparison. Okay.

Some of these are low, and I'll get into those. I named one of them on the previous slide, and one will appear here as to a low virus. The next slide is slide 14. So, this is HI. This is getting into specific hemagglutination inhibition data. Highlighted in gold, I'll walk you through this now, are antisera to the previous vaccine virus for the Southern Hemisphere, the Michigan/45 virus. And on the righthand side is the reference antigen group.

So, you can see A/Michigan/45, clade 6B1. It

has a homologous titer of 1280 to the MDCK cultivar. So that's the very top row. And Michigan/45/6B1 egg virus, it has a homologous titer of 1280, so that's in the second column there. So, you can see that you're comparing the cell versus the egg in those reactivity patterns.

And if we walk down that reference antigen column, then we run into the Brisbane/02, which is the recommendation for the Northern Hemisphere that we're getting this year. It's a 6B1-A virus, so it's in that group that I pointed out that represents basically all the viruses circulating now. It has a homologous titer of 1280 for the cell cultivar and 2560 for the egg cultivar. What you can see is that those two viruses cross-react with each other very well in ferret antisera. And then we look at the IVR/190. This is a Brisbane/02 reassortant virus, so that's the column headed by E3/D8. It should be E8, actually -- IVR/190. And there it has a homologous titer of 2560.

And now, we get into a Darwin virus. This is in this P5 group that was at the top of the tree that I

showed you, which was more rapidly expanding. And we're seeing a lot of those viruses within the H1N1 groups. That Darwin/6 sera has a homologous titer of 640 and also cross-reacts with the other reference antisera. Darwin/102 is in this P2 group but not only that. It has a substitution at position 156 to a K.

So, we did see a smattering, about three percent of the viruses circulating are like this Darwin/102. And ferrets antigenically distinguished this group of viruses very well. You can see that its titer is 640, its homologous titer -- so if you follow that very bottom line across, it's 640. But it's not reacting very well with the reference viruses above it, all these different groups that I walked through, nor is it recognizing the test antigens very well that are circulating.

So, we'll just now go down into the test antigens. And what you can see is that the Michigan/45 viruses, both the cell and the egg, along with the Brisbane/02 viruses, cell and egg, really react very well with the majority of these viruses that are out

there circulating. And where you see on that is a low reactor like this one Malaysia virus at less than 80, this is generally a virus that has a substitution at position 156. So, we saw a few of those substitutions at position 156, like this Darwin/102 has, in viruses circulating. And all the collaborating centers had a few of these, and they all characterized very similarly, not reacting well with the ferret antisera. But when you make sera against them, it reacts very well with those. But those viruses don't produce antisera that reacts with the other circulating viruses. All right.

So now I'm going to move to the next slide. This is a little easier.

DR. MEISSNER: I apologize. Can I just -- I just want to make sure I understand this slide.

DR. WENTWORTH: I think that's very fine. Don't apologize. Let's make sure.

DR. MEISSNER: So, as I look at these figures, it appears that there's only about a twofold difference between the egg-based and the cell-based strains. So,

it doesn't seem like that's very much. Is that correct?

DR. WENTWORTH: That's correct. With the H1N1 viruses, we don't see as much of a difference, antigenic distinction between the egg and the cell viruses. That's not true for all egg viruses. But typically, those that are selected for vaccine production are selected because they don't have as much difference from cell viruses. So, in this case, the Michigan/45 is a very good egg virus and same with the Brisbane/02.

DR. MEISSNER: So that's encouraging because it means that the egg-based vaccines are pretty good in comparison to the cell-based.

DR. WENTWORTH: Yeah. In this context with the H1N1 viruses, you're interpreting this H1 correctly. And the ferrets don't really notice too much of a difference, and I will show you some human serology data with egg-based only to illustrate how it works in humans against viruses that are circulating. Generally, these egg-based viruses acquire one to two

amino acid substitutions, one of them typically at 223, which is right in the receptor binding pocket. So, it tends not to have dramatic impact on the antigenicity.

DR. MEISSNER: Thanks very much.

DR. WENTWORTH: And as I said, those egg viruses that are isolated but do have an impact on antigenicity usually aren't further progressed through reassortment or anything like that. They're kind of eliminated by the collaborating centers.

DR. MEISSNER: Okay.

DR. WENTWORTH: Okay. Great question. Okay. So, I'm going to move to slide 15. This is a little easier on the eyes. It's antigenic cartography. As Dr. Weir mentioned, I would show some of this. What this is, is taking those multiple HI tables and converting them into a more cartographic look where you can see how related viruses are and the fold reductions they have from each other.

And as was just pointed out, the egg and the cell in this case are relatively antigenically close, so the Michigan/45 egg is shown in the blue oblong

thing. And actually, the cell isn't shown on here, but it would be right on top of it. And the Brisbane/02 egg is shown as the green egg-shaped dot. And all the small blue dots indicate viruses that are circulating out there. And they all have this 156N, which is the, quote/unquote, "wild type amino acid" at position 156 for the vast majority of H1N1 viruses that are cocirculating.

And what you can see here and appreciate is the 156K substitution and what that does to the antigenicity using a ferret antisera as a readout and how it moves the virus to many-fold, eightfold or more, away from the vaccine viruses. But basically, those are the only viruses that we've seen that had antigenic impacts using ferret antisera. And that is representing about three percent at their peak of the viruses that were cocirculating over this period.

So, if we move to the next slide, this is a slide illustrating the human serum that is used for the following slides. And I think it's important. So, we have the serum from the U.S., which is the top group

here of the population -- the U.S. population. And there, we have multiple age cohorts of what we call a pediatric, which is 11 to 33 months; and older pediatric, which is really young adults in some cases, 9- to 16-year-olds; adults 18 to 47; the older adults, which is the 50 to 65-year-old window; and what's considered elderly, and that's 65 and older. Sixty-five to 82 is where we collected the serum. And this is post-vaccination serum that's collected, and the vaccine components used here are listed in this column.

We used A/Singapore/INFIMH/16-0019 from 2016. It's also the reassortant IVR186. So that's the previous recommended vaccine -- the Michigan/45(H1N1), the B/Phuket/3073, and a B/Maryland/15/BX69A reassortant. And this is representative -- this is a Colorado-like virus that Dr. Weir mentioned earlier that was in the previous strain recommendation. And I will describe that a bit more when I get into the influenza Bs. I'll remind you about it. The Australian serum panel, we only have an adult, which is 22 to 64, so it's basically just a wider age range that

we have for the U.S. serum panel, and an elderly, 65 to 82, which is the same age range as we have for the U.S. Okay.

Now we move to the next slide. This is looking at the human serology and we're looking at post-vaccination hemagglutination, geometric mean titers -- that's what GMT stands for. Sorry for the acronym -- relative to the cell propagated Michigan/45 2015-like virus.

So, you can see here the cell is the first column. MI45/MDCK is listed. And we're setting the pediatric population to 100, the older pediatric to 100, the adult to 100, and the elderly to 100. And then our 50 percent geometric mean line is the red dotted line that goes across this chart. So, we like to see viruses to be above that line if we're going to have better optimal vaccine. And those that are reacting poorly would be more below that line. So, they are showing a reduction in geometric mean titers. A significant reduction would be well below that line, and what you're seeing here is some reduction.

So, if we now compare it to the Michigan/45 egg, we actually get great reactivity compared to the cell. This of course is the virus people are actually immunized with or represents the virus people are actually immunized with. Then we have Idaho/7. So, this, I mentioned earlier, is the recommended vaccine for the Northern Hemisphere for cell vaccines. So, it's a cell-base version of the Brisbane/02 egg-based vaccine. And you can see the human sera doesn't recognize this as well.

Remember these people were vaccinated with Michigan/45, and this is part of the rationale for why the vaccine was changed in the spring. So, I'm just kind of reiterating that. You might have seen this before when Dr. Katz presented. But we've repeated this study for this particular strain selection. So, this is consistent with what we saw in the spring.

The Idaho/7 viruses particularly in the pediatric population show a reduction. The older pediatric, you can see it hovers above the 50 percent threshold. And they do pretty well against many of the

other viruses circulating. The adults, again, it's right on the line.

And now the adult we can see, now, the addition of the gold bars, which is the serum from Australians. And again, against the MDCK we set that. You get 100 percent against the egg. We're seeing a little bit of a drop. In this case, it's a little different than the U.S. serum. But then it drops more significantly with the Idaho/7, the Wisconsin/505, the Iowa/33, Iowa/12, and Maine/38.

So now that we kind of have a baseline, I'll walk through what these other viruses do. So, the base of the entire 6B1A group, with a 183P substitution, is like this Idaho/7. And now, if we move to the Wisconsin/505, if you recollect that was at that top of the tree, so it's also a 183P virus. But it has additional substitutions, one at 129 from an asparagine to an aspartic acid, so an N129D. And it also has a thraneen to an isoleucine at position 185, which, of course, is very close to position 183.

This was included as a serology antigen

because we wanted to know if there was further antigenic evolution from human sera vaccinated with the egg. And what you can see is it reacts with a very similar pattern as to what we saw with the Idaho/7, so not a more significant reduction in reactivity. The Iowa/33 is another subgroup in the 183P-5, and this has a distinctive substitution at position 130 that distinguishes it from the Wisconsin/505-like viruses. We also saw pretty good reactivity. And again, the older pediatric population is doing very well against the H1N1 PDM09 viruses. And I think you can appreciate that here.

Then, if we look at the Australian sera, we can see reductions with the Idaho/7 and Wisconsin/505, along with the Iowa/33. And I'll get into Iowa/12 and Maine/38 in a minute. Looking at the older adults, that's a similar story and the elderly. They actually are -- the sera from elderly look a little bit more like sera from the pediatric population than they do the older pediatric or adult in both the Australian and U.S. panels.

Now let me just tell you briefly -- I'm sorry I'm spending a lot of time on this slide, but I think it's very important, particularly with the H1N1 viruses, to be looking at the human serologic data. The Iowa/12 is one of these 183P-5 groups, but it also has a substitution at position 156.

So, we know the ferret sera -- when I immunize a ferret with a 183P-5, like Michigan, it won't react very well with a 156-substitution variant. So, this represents one of the 156 substitution variants groups we were seeing, 156D. And again, it is reduced compared to Michigan/45, but it's not really more reduced than the Idaho/7 or the Wisconsin/505 or the Iowa/33. That's true basically going down the column in all the various age group serum panels.

You can actually see older folks, like adults and the elderly particularly in Australia sera, may do a little bit better in that group than in some of the other groups. But they're very similar, as well, across the board.

Now, if we go to Maine/38, that's the 156K

substitution. And again, we see a reduction there. That's the one that maybe has a stronger impact even in human sera. So you can see that going down. We didn't have enough human sera to test that with the older adult population, which is why you don't see any bars in that. All right. I'll pause there for a second in case there's a question, and then I'll move to the next slide. Okay.

This slide summarizes the H1N1 PDM09 virus groups, and H1N1 virus that's circulating globally predominated in many countries. And I showed you that earlier: Africa, Asia, Europe, and South America. Genetically, nearly all of the viruses fall into this 6B1.A clade, which have these characteristic substitutions of S74R, S164T, and I295B. There are several cocirculating clades that have S183P as a defining amino acid characteristic. The majority recently are in the S183P-5 group and also share amino acid substitutions N129D and T185I. And that Wisconsin/505 virus that we tested in a variety of our assays is a representative of that group.

The Northern Hemisphere vaccine viruses are Brisbane/2 for the egg-based and Idaho/7 for the cell based, are 6B1A with S183P substitutions. And they were tested in the human serum panels and in the ferret serum panels. Antigenic analysis with ferret antisera demonstrates they're indistinguishable from egg and cell culture propagated in Michigan/45 viruses.

So, the viruses circulating currently aren't distinguished well by ferret antisera. They're also undistinguished from egg propagated in Brisbane/02 and cell propagated Idaho/7, the newer vaccine viruses for the Northern Hemisphere. With the human serology studies, the post-vaccination HI geometric mean titers against recent representative 6B1A, plus S183P, were reduced compared to those of cell propagated Michigan/45 virus. All right.

I'm going to turn our attention to H3N2 viruses, moving just right past that title slide or separating slide H3N2 to slide 20. Thank you.

This is now illustrating the H3N2 viruses detected by GISRS, 2019 in red again. And you can see,

again, a peak towards the beginning of the year. But if you remember that peak from the H1N1, this one peaks a little bit later. That H1N1 peaked around week four, and this one peaked around week seven.

If we move to the next slide, this shows our activity globally, widespread outbreaks again in North America and in South America, parts of Africa and Eastern Europe, Asia, and quite a significant outbreak -- I think everyone's aware of widespread activity in Australia. If we move to the next slide, this is a phylogenetic tree. This is a very dense phylogenetic tree provided by colleagues at the University of Cambridge. I like it because it's a high-level view. I'll go into a little bit deeper level view.

It illustrates the various clades circulating in the black portions of the tree itself, along with the regions where the viruses are isolated, represented by the heatmap on the right. So North America's in blue. So, you can see a bunch of blue dashes at the top left-hand column there that become more and more pronounced as we move from late 2018 to 2019. I

apologize. You might not be able to read that. But it's basically looking from a couple years back to more recently. The very far righthand side are what are the most recent viruses circulating by month. And then the color-coding -- you can see the color-coding of the world there on the lower left-hand corner.

So, the very top of this tree represents 3C3a clade viruses, which you can see have been around for quite a long time. They took a bit of a hiatus and then reemerged very strongly during our season last season. These are 3C3a viruses that emerged about -- to begin to really increase in November but really came on strong in December, January, February in our season last year.

Then we have down a little bit below that group are the 2A2 viruses, represented by that black bar on the left. You can see they were heavily predominated a few seasons ago and have been reducing over the course of time. So, you can see again the blue representing United States, where they circulated. They caused a big part of our season previously.

Then we have 2A1b viruses, which you can see that tree how it looks. There are a few subgroups within the 2A1b viruses, the primary subgroups being some that have a 135K substitution. So, I've illustrated that by this small blue line, which makes up part of the large black line illustrating the 2A1b viruses. And these you can see are more recently circulating globally, the green in Europe, the orange in Africa, Middle East purple, Russia, Southeast Asia, et cetera, and Oceana.

And then we have a relatively new group of virus. You can see they didn't exist in a time series of the tree until we get to very recent months. These are a subgroup of the 135K viruses that have three additional substitutions, which I've listed there: 137F, 138S, and F193S. And those really only have circulated in Asia and are very recent.

And then we have a 131K subgroup of the 2A1b viruses, and those are at the very bottom of this particular tree. And you can see they weren't circulating early and have really started to increase

more recently and are dominating within the 2A1b group globally. So, we've had -- an easier way to think about this is a relative decrease of the -- within the 2A1bs, we've had a decrease of the 135Ks and an increase of the 131Ks.

If we move to the next slide, this is hopefully a little closer up view of the tree. Again, it still represents a lot of sequences, but it's a tree from our collaborating center to try to orient you with some of the viruses that I'll be showing you data from. So, the 2019/20 Northern Hemisphere vaccine virus was name, and, as Dr. Weir said, it's a 3C3a virus called A/Kansas/14/2017. So that's at the bottom of this particular tree. These were at the top of the last tree.

I apologize for changing the orientation of the evolution. Again, they're color coded. The dots on the tree are color coded by the geographic region in which the viruses are circulating. So you can see, primarily, 3C3a's in North America and Europe, for example.

The Southern Hemisphere vaccine virus that we're discussing today whether we should keep it or change it is this A/Switzerland/8060 virus, which you can see right in the smack middle of the tree. It's a 2A2 virus, which we now don't see very many viruses circulating from this group. They've really continued to decrease and been taken over by both the 3A and the 2A1 viruses, which are more towards the top of the tree.

So those viruses I just described, 2A1b, 135K, are the next in the series, and they're represented here. Then we have 2A1b 131K viruses. At the base of that group is this Iowa/60 virus. More partway up that group is a Montana/18 virus. This has all the substitutions that Iowa/60 has; plus, it has a Q197R substitution.

And then the more evolutionarily advanced virus is this Hawaii virus, Hawaii/42, near the top of that tree. Hopefully you can see it on your slide decks that you have personally. And those are 2A1b. They're all 2A1b 131K viruses. Of course, the previous

Northern Hemisphere vaccine virus was a Singapore, which is the black virus name right above the Southern Hemisphere vaccine, the Switzerland virus. Okay.

We move to the next slide. This shows you the global circulation of the H3N2 HA clades. So I want to get a couple of points across with this slide. It's a visual slide illustrating that, while there is multiple cocirculating subclades of the H3N2 viruses, primarily the major clades being 3C2a and 3C3a viruses. And then within the 3C2a, there's all these various subclades that I just walked through. So what you can see is, in the Western Hemisphere, we have a lot more 3A viruses and fewer 2A1b viruses. And where we do have 2A1bs we have a mixture of 2A1b 135Ks and 2A1b 131K viruses.

And if we focus in on the southern portion of that, South America, you can see there's -- like North America, they do have quite a bit of 3C3a viruses, some 2A1b 135K viruses, and some 2A1b 131K viruses. As you move east, you can see that Europe has a bit more of a mixture and Africa with a lot more 135K viruses, as well as 2A3 and 2A4 viruses, which are quite old

evolutionarily speaking. They don't really -- we don't see them circulating in other regions of the world right now for the most part. They certainly don't dominate the proportion of viruses.

And then, as you move further east, we see predominately 131 and 135K viruses. And Australia had just a really strong amount of 131, whereas Asia saw more 135K viruses. So, it's a geographically varying group of viruses that are co-circulating. If I were to show you this with the H1N1s, they would all be basically very similar to each other. So, we move to the next slide.

This is now showing the reactivity with ferret antisera against the current recommended southern vaccine -- Southern Hemisphere vaccine, the Switzerland/8060 egg virus. The collaborate center that did the testing is listed on the left, CNIC, for example. So, there are 30 percent that are like that and 70 percent that are considered low, which would be eightfold or greater reduction in homologous titer. The Crick -- only three percent considered like and 97

percent low. VIDRL, 13, so two percent considered like and 98 percent considered low.

And this is in HI assays. And remember, there's going to be regional differences on the viruses that are being tested. So, these don't necessarily represent differences in the assays done by different groups. It more represents differences in the viruses that are circulating in various regions.

Now here we're looking at the next slide, 26, the H3 -- there we go -- the H3N2 reactivity like versus low. Now, this is in virus neutralization assays instead of hemagglutination inhibition assays. As you've probably heard before, the H3 viruses no longer agglutinate red blood cells efficiently, so we have to use a little bit more cumbersome virus neutralization assays for antigenic analysis.

These are not as high throughput, but they provide strong data. So, we've switched, particularly at the CDC, to primarily using these only. And again, on the green side we're comparing against the cell virus, and on the blue side we're comparing against the

egg virus.

So you can see the CDC, this one is 8060, about 17 percent considered like and 83 percent low. NIID in Japan, three percent like and 97 percent low; and Melbourne VIDRL in Australia, 93 percent considered like and seven percent low. With the egg, this is a common trend where we see the egg antigen doesn't induce immunity that cross protects against the circulating strains as well.

And you can see that here where it moves -- like for the CDC, it moves from 17 percent like to only nine percent like and 91 percent low. And for other CCs, it's even worse where 100 percent are low, 94, 99, 98. Move to the next slide. This is --

DR. JANES: Dr. Wentworth?

DR. WENTWORTH: Yeah. Go ahead.

DR. JANES: Dr. Wentworth, this is Holly Janes. Can I pop in a question real quick?

DR. WENTWORTH: Shoot.

DR. JANES: Following up on your comment about whether or not these differences amongst the sites are

differences in the assays between the sites or differences in the viruses that are selected and tested at different sites. I'm thinking that they must be more attributable to the differences in the viruses across the sites because it seems that the characterization of what a like response is versus a low response is site specific. In other words, it's based on comparing the responses to the vaccine virus. Is that correct?

DR. WENTWORTH: That is correct. For the most part, that is correct. So, of course you can see differences in the ferret sera because we don't all use the same ferret sera. So, there can be a lot of variation. And when you pile all the data together like this in a summary format, you may miss a few things. But you've got the take home point which is what I showed you previously with that phylogeography illustrating the different phylogenetic groups of HA and where they're circulating.

You can imagine that, if you have a lot of a certain type of virus in your region and that's what

you're testing, it's going to skew the data in a way. It's going to show that you're not reacting or reacting better to the current vaccine virus. So I think both things are factors, but the take home point is a lot of these represent regional differences in the viruses circulating, as you surmised.

DR. JANES: Thank you.

DR. WENTWORTH: All right. We move to slide 27. This is the Kansas/14 now. This is the Northern Hemisphere strain recommendation, again, the cell in green, the egg version in blue. And this actually brings home that same point where if you remember, in North America, we were seeing a lot more 3C3a-like viruses. And you can see that 75 percent of them -- 78 percent of the viruses we've tested are considered like the Kansas/14 and 22 percent considered low. And this shifts a bit to 52 percent like and 48 percent low when we use the antigen from egg cultivar.

CNIC is seeing a little bit different trend where they are seeing less like, and they don't have very many 3C3A viruses in China, and a lot lower. And

I won't walk you through each row, but you can see this trend. And Crick is seeing more similar, so this is in London -- a little bit more similar pattern to ours but only 37 percent like and 63 percent low to the cell. When we're looking for antigenic drift, we focus primarily on this cell reactivity pattern.

And then we're of course interested in how the vaccine virus that's used in most of the vaccines, which is the egg virus, also performs. So, we're always looking for two things: one, drift. Is there enough drift to warrant a change in the vaccine? And how well does the current vaccine virus cover all the viruses that are cocirculating, no matter which group they're in? Okay.

I've moved to the next slide. I think I'm taking too long. Okay. The antigenic analysis of the viruses -- now, this is getting to a detailed view of what we are looking at. This is ferret antisera. I'm going to take a little bit of time to walk you through this. Nebraska/2 represents a clade 282 virus. This is the qualified manufacturing cell seed candidate,

Nebraska/2. So, it represents the Southern Hemisphere recommendation of Switzerland/8060 as a cell-based antigen. You can see it has a very high homologous titer, a great antigen of 2480. But this reacts very well with 2A2 viruses but shows strong reductions against all the other clades.

North Carolina/4 is the next virus down and is the 2A1 virus. So, this is a rather older virus. This was the cell candidate vaccine virus previously -- is North Carolina/4. And it has a 2560 titer but, again, a good reduction from the homologous titer. And I won't belabor the current vaccine because it's very clear we see strong reductions against all the reference viruses that are in the various 2A1b subgroups, as well as 3A viruses. And the test viruses are eightfold or greater in general. And then we see very strong reductions when we get into the 3A viruses.

If we move to the next column, this is the North Carolina/4 antisera to that virus. The homologous titer is bold and underlined, 2560. You can see this virus reacts well with kind of both the 2A2

virus --even though those are antigenically distinct, it does cross react well with those -- and covers all these various flavors of the 2A1bs, 2A1b 131K viruses such as the Iowa/60 or Arizona/45, as well as the Wisconsin/327, which is a 2A1b 135K group virus, and North Carolina/36, which is a 135K like virus. Where you do see the reduction now in that is with the 3A viruses, showing that they're very antigenically distinct. So all these 2A viruses are relatively antigenically similar when compared by ferret antisera, and the major antigenically distinct virus is being the 3A.

Iowa/60 now represents the base of this 131K group. And it has a homologous titer of 5120. Again, it cross reacts with earlier progenitor viruses such as North Carolina and further advanced viruses, such as Wisconsin/327, which is a different group then the 135K viruses, but doesn't cross react well with the 3C3a viruses. And then when you look at the test viruses, that same pattern holds true, and you can just kind of scan down that column. We even have a few from, for

example, the Congo. So the top of that group are 131K viruses, again, great reactivity with the homologous antigens, and then the 135K groups. And then we have a couple from Congo and Mali. Remember I showed you Africa had some of the older viruses still circulating: 2A3 viruses. Again, those react okay with serum from a 131K virus, Iowa/60. And it's not until you get to the 3A viruses that you see these more dramatic reductions.

Arizona/45 is a qualified manufacturing cell isolate that is very similar to Iowa/60 in its HA, and it has a very similar pattern. Then we get to the 2A1b 135K sera. We have Wisconsin/327 and North Carolina/36. Again, what you can see is this cross reacts well with the 131K viruses, as well as just the standard 2A1 viruses. It does not react well with the 3A virus.

And then if we look at the 3A antigen, this is Indiana/8. This is sera from the seed for the qualified manufacturing cell candidate for 3A viruses. So, this is a Kansas-like virus. It's homologous titer is 2560. You can see it has some reductions but not as

significant, I think, as the other way around with the test antigen and then, of course, recognizes very well the test antigens within the 3C3a viruses.

Then we move to the next slide. This is now looking at FRA data from the Melbourne CC. Again, we have a similar layout where we have the Switzerland/8060 virus, both a cell and an egg pair. The sera for those are shown in gold. And then we have some 131K representatives, a 135K representative, and some 3A viruses. And what you can see is that the 8060, again, has a high homologous titer here for the most part and, particularly, the egg virus with a 10240. And we see significant reductions against all the test viruses that are circulating. These are very recent test viruses from Melbourne, so they hadn't genetically characterized them well yet. But the majority of them will be 131K viruses with, I think, a few 3A intermixed in there.

Then we have Newcastle/82. So now we're looking at a couple of the better egg performing viruses compared with their cell pairs that were

available. Newcastle/82, which is a cell versus the egg, in the next column with pink, and you can see their homologous titer is 640 for the cell and how well it covers all the test antigens circulating, with the exception of some of those at the bottom, again, with a pattern. So, for example, the Perth/1015 has an antigenic pattern similar to what you would see with a 3A virus.

Also, South Australia/34 is another 131K virus where there's an egg-cell pair. You can see the cell homologous titer is 2560. The egg homologous titer is 5120. Of course, the cell reacts quite well with the majority of the test antigens, and then the egg does a little bit more poorly. But what you can appreciate is the raw titer is fairly high. So, it's still like a 640 in many of the test antigens ranging from 160 to 640, really, in antigens likely in that group.

Then we have the SIAT 135K virus. This one is the Victoria/653. Again, the cell antigen is 5120, and it reacts well with most of the test antigens. This is similar to what I showed you with the FRA previously

and Kansas/14 cell versus egg, the 1280 titer reacting with a little bit more reductions than the 2a1bs. Again, the majority of these test antigens being 2a1b 131K viruses.

Move to the next slide. This is the antigenic cartography. This is using data from the CC in Atlanta, our FRA data, where Iowa/60, a cell version of the virus -- of the 131K viruses -- where that is positioned and all the viruses that are cocirculating. In the red colors are 2A viruses and 2A1b, for example, as well as a few 2A2s. And they're a little bit more antigenically distinct -- versus the Kansas cell and egg pair, which are the test viruses that are 3A are the green dots. And the cell virus is the blue round dot, and the egg virus is the blue oval.

If we move to the next slide, this is showing cartography now from CC Melbourne by HI data using an egg-cell pair, South Australia/34, versus the Kansas/14 egg-cell pair. And what you can see is a lot of the viruses, again, the South Australia/24 is in a good position here, right in the middle of the cell of the

major cluster of viruses that are circulating, a lot of them being 2A1b with 131K, and the South Australia egg.

If we move to the next slide, now we're looking at the human serology data against using the egg as the 100 percent cutoff. So people were vaccinated. And now we're looking at sera from Australia. They were vaccinated with the Switzerland/8060. And the reference antigen here that we're comparing to is the Switzerland egg. And what you can easily appreciate is all the test antigens that are cell-oriented test antigens fall below that 50 percent geometric mean cutoff. It's very hard to discern if there's any difference between, say, a 2A1 virus like Singapore/INFIMHCF cell virus, which is a 2A1, and those 2A1b viruses that have the 131K or 135K or 3A. And what you can appreciate is 3A has some reductions.

Both the last two columns have the more significant reductions, and it'll be easier to see on the next slide. When we compare to the cell, this is slide 33. Now we're setting the reactivity to the cell

antigen at 100 percent, and you can see that the egg goes up even higher than that because people aren't immunized with the egg cultivar generally. The Singapore 2A1 still has -- serum against the Switzerland/86C is reacting but with reduced titers to the Singapore 2A1 131K viruses and doesn't show a real marked reduction until you get to this Hongkong/45, which I didn't discuss very much previously except to mention that we had that new group of Asian viruses that have some additional substitutions, this S137F, 138S, and F193S. So that one being more antigenically distinct by human sera, and the other one that falls fairly low, particularly with the elderly, are the 3C3a viruses. And you can easily appreciate that with the serum from the elderly cohort.

We move to the next slide. The summary for the H3N2 viruses is that there's regional heterogeneity in the clade circulation, the 2A1b subgroups -- there's many of them cocirculating. The subgroup 2A1b 131K predominated in Oceana; whereas, the subgroup 135K did in Asia. And we saw the emergence of this newer

subgroup, the 137, 138, and 193 substitutions, beginning to increase in Asia. The 3C3a viruses are primarily circulating in the Americas, and 3C2a2 viruses, which the current Southern Hemisphere vaccine is a member of, have decreased markedly.

Antigenic characteristics with ferret antisera illustrated that the 2A2 viruses poorly inhibited 2A1b and 3A viruses; whereas, serum from 2A1b viruses poorly inhibits 3C3a viruses, which clearly an antigenic distinction between those two groups. However, the 2A1b virus subgroups are all quite antigenically similar with ferret antisera. We did see some reductions in 2A1b 135K viruses that also have the S137S, 138S, and 193S. The 3C3a viruses are antigenically similar to each other, and antisera to 3C3a viruses poorly inhibits the 3C2a viruses. So, we see eightfold or greater reductions frequently with those.

If we move to slide 35, the human serology studies should illustrate the individuals vaccinated with Switzerland/8060 vaccine viruses had reductions in

the geometric mean HI and virus neutralization titers against both 2A1b and 3C3a viruses compared to titers against the egg propagated virus. When we look at the cell propagated as the comparator, reductions in the geometric mean against 3A viruses were more pronounced than most of the 2A1b viruses, with the exception of the 135K group that had the additional substitutions. Okay.

Now, we're going to transition to the influenza B viruses. I will move a little more rapidly because you all are onboard now. The 2A1b, we're going to go to slide 37. This is illustrating the activity. As I showed you very early on, we didn't see as much influenza B activity -- local activities in many areas around the world, some regional outbreaks in South America and Africa and some in New Zealand. The number of B viruses detected, if we move to the next slide, by GISRS are illustrated here, again, the red line illustrating what I just said. We really didn't see a huge amount of influenza B circulation over the past month.

We move to the next slide. This is the antigenic characterization by CCs over the past three reporting periods, again, the most recent being the green illustrating where people have been able to collect enough viruses to do a lot of antigenic characterization, really significant amounts done by CNIC in this timeframe, which is the China CDC. If we move to the next slide, influenza B lineage distribution and percentage. So, I had mentioned this earlier, and this is a little more detailed view of it where we saw about seven percent of the B viruses circulating are the B/Yamagata lineage; whereas, 93 percent are B/Victoria.

The breakdown by region is shown on the right, with Asia being very heavy in B/Victoria. North America is a bit askew because we do a right size program here where we actually ask for more of the under-representative viruses in our surveillance efforts. Oceana primarily B/Victoria, South America more of a mix, et cetera. We move to the next slide. We'll go specifically to the B/Victoria viruses. Move

to slide 42, next slide after that. Thank you.

Looking specifically at the B/Victoria viruses now, we can break these down into three major groups: the V1A viruses. These are the older viruses that circulated for quite a long time. The V182 del viruses, this is the next older virus group, and they have two deletions in the -- amino acid deletions in the hemagglutinin gene. And that did impact antigenicity, and this is the group that was included in the vaccine. Then we have the V183 del group, which is emerging now to be more dominate and overtaking the two del group. The breakdown by collaborating center I'm not going to walk through, but, again, there are some regional difference in the phylogeography.

If we move to the next slide, this is illustrating some of that -- again, a large tree looking at all the viruses circulating. And I'll try to orient you to this. The older viruses here being at the top of the tree, you can see that in the time series to the right, the heatmap, and the newer viruses being both the triple deletion and the double deletion

variants that are more towards the bottom. Like two-thirds of the way down is the newest triple deletion group and then at the very bottom is the double deletion group.

What you can appreciate is there were triple deletion viruses that evolved through parallel evolution quite early on. However, these died out and were overtaken by the double deletion group. And more recently, we had this group of triple deletions that are the two-thirds of the way down the tree that evolved and more rapidly increased. And you can see their global dissemination there, as well, by the color coding. Again, the double deletion seen very heavily in North America. You can see that's why you can see a lot of the blue there, really evolving in the Americas to start with and then spreading. All right.

Moving to the next slide, this is the like versus low that you are now familiar with the color coding, cell versus egg, green versus blue. Again, now looking at the older vaccine virus, the Brisbane/60, we have very few that are like, 81 percent considered low.

Trends are very similar by multiple collaborating centers in this case. The egg variant has a similar pattern, a little bit more significant reduction, so increase in the number of those considered low.

The next slide, this is a Victoria-like versus low now against the contemporary vaccine virus. The double deletion virus called B/Colorado/6 is the like virus that we want to name. And again with the CDC where we're seeing a lot of double deletion variants, 78 percent are considered like, 22 percent considered low. CNIC had a lot of reactivity with the double deletion virus in their hands, even though they're seeing considerable triple deletion viruses but some reductions when they used the egg cultivar, down to 45 percent like and 55 percent low. Crick pretty similar pattern with the CDC. Same with the NIID in Japan and VIDRL in Australia.

We move to the next slide. This is going right into the antigenic cartography to give you a high-level view of what's going on. The Colorado, this is the double deletion viruses, are shown in blue

there, the egg and the cell, oval versus round. And the circulating double deletion viruses are kind of that orange color. The triple deletion viruses are a purple color. And then we have a cell candidate, Washington/2 2019, that is a triple deletion representative. And you can see how well antisera to that corresponds in clusters with that group of viruses.

To drill into the data with some more detail, we can move to the next slide, slide 47. This slide really illustrates the antigenic patterns that you can see. You can focus first on the reference virus, the older vaccine virus, Brisbane/60 from 2008, egg and cell pairs. You can see a good homologous titers and a good high homologous titer but then have significant reductions with the V1A.1 and the V1A3 del viruses, which represent triple deletion variants. Then when we look at the V1A.1 virus, the more contemporary vaccine virus, it has a homologous titer of 160 with four- and eightfold reductions to viruses that are circulating. That's the egg counterpart versus the cell, which is

this Iowa/6 virus. That has a homologous titer of 320, again covering its group, the double deletion mutants, which are circled kind of squared in blue, fairly well as well as progenitor viruses like Brisbane/60 okay and showing more reductions to the triple deletion virus represented by the Washington/2.

And then the Washington/2 viruses are squared purple where you can see, again, the egg with a homologous titer of 320 and the cell with a homologous titer of 640. Again, this is a pretty good egg-cell pair. There were not significant reductions between the two. And you can see they cover the viruses in the V183 del group fairly well and don't react as well with viruses in either the V1A.1, which have the double deletion, or the progenitor virus, the V1A. Okay.

We move to the next slide. This is now looking at human sera from folks that were vaccinated with the Colorado/2-like virus. We're setting it at 100 percent with the Iowa/6 qualified manufacturing cell vaccine virus as a cell version of the Colorado egg. Colorado/6 egg is the next column over. So, we

can see in the different populations, the pediatric, older adult, adult -- I mean older pediatric, adult, older adult, and elderly. And again, the orange bars represent serum from Australia, but they have the same vaccine in this case. You can see that it's actually quite good news. The Colorado egg is the immunogen. Of course, when we set the cell to 100, we see good reactivity across the board.

Now, comparing to a V1A virus, V1A.1 virus, an older virus, a V1A/Maryland/27 also gets -- we see good cross reactivity in those older viruses. And then the newest groups of viruses, Louisiana/16, represents one of the V1A three deletion groups, and Washington/2 represents the more recent three deletion group that has really taken off. And you can see humans vaccinated with the Colorado/6 antigen actually react quite well to the newer three deletion groups, which this contrasts a bit with what ferrets do, naïve ferrets versus, of course, humans that have seen many influenza Bs in their lifetime.

That pattern holds true across the different

age groups, so I don't think I'm going to walk through it. I don't think there's anything to glean other than to know the adults really probably will do better than the pediatric in this case. But you can see pediatric do pretty darn well.

Next slide, we're going to move into the B/Yamagata viruses. I will be fairly brief here because, as I mentioned, there hasn't been tons of circulation of this virus. What you can appreciate, if we're on slide 50 now, again, a very large phylogenetic tree showing the distribution of viruses over time and their evolution, the bottom of the tree being the most recent. So, it's going from older viruses at the top to the more resent at the bottom, generally speaking. And then, you can see the most recent viruses by the tick marks on the heat map, the far right.

And what we're seeing is a fairly monophyletic evolution pattern where a lot of these viruses are really very closely related to each other. That's why you get these very flat vertical lines where there's not as much branching. There's not a specific

geographic region where a particular subgroup is circulating, for the most part.

If we move to the next slide, this is like versus low in hemagglutination assays to the current vaccine virus, B/Phuket/3073, again, the cell on the left and under the green bar. Basically, 100 percent of the CDC, 94 for CNIC, only 33 percent for Crick, and the other two groups looking more like CDC and CNIC. Then, when we look at the egg, Crick actually had a little better path with the egg virus in that they see pretty good protection with those viruses. And we see some reduction by CDC, CNIC, and VIDRL, where we saw instead of 100 percent reactivity, for example, for the CDC, 67 percent considered like and 33 percent considered low.

The next slide, on slide 52, this consolidates a lot of HI data, which I decided not to walk through because it looks very similar to what you've seen before. From September 2018 to 2019, you can see the viruses that circulated there are the yellow dots, and they're really just directly overlapping with the blue

dots, which circulated previously from August 2017 to August 2018. The Phuket cell is shown in the red circle, and the Phuket egg is shown in the green. So, you can see that that Phuket egg, again, is a little antigenically different than the cell and pushed a little further and ultimately explains the summary that I just presented where we saw more reductions against the egg sera than we saw against the cell sera.

If we move to slide 53, this is human serology against Yamagata, looking only at the Australia panel now in the adults and the elderly at the top versus bottom sets of bars. The Phuket setting at 100 percent to the Phuket cell cultivar. You can see we see pretty good reactivity with more recent viruses representatives that are circulating, along with the current Phuket virus itself.

If we move to the next slide, which is 54, this is a summary of influenza B in total. So, I have two slides on this. In general, influenza B virus is circulated at low levels globally. We saw a lower proportion than A viruses except in very few countries

in Southeast Asia. We saw B/Yamagata/16, 88, and B/Victoria/287 lineage viruses that cocirculated. So, we shorthand those to B/Vic and B/Yam or B/Yam and B/Vic respectively. The B/Victoria lineage predominated, except in parts of South America.

Genetically, if we move to the next bit about the lineage for B/Victoria viruses, the HA genes were all clade 1A, but they're not homogeneous. Viruses with deletions in the hemagglutinin predominates now, with those -- with the 162 to 164 deletion now seen in the majority.

Previously, we saw only the double deletion variants, so 162, 163 in the majority. Ferret antisera to the cell and egg propagated B/Colorado-like viruses, which are the double deletion group, well inhibited V1A.1, which are the two deletion group viruses, but had reduced inhibition of either the three del or older viruses that lack the deletion entirely. Ferret antisera raised against the cell and propagated triple deletion viruses, for example the Washington/2 virus from 2019, well inhibited all the triple deletion

viruses out there that we tested.

And post-vaccination human sera to V1A.1 antigens, so again, the double deletion virus, recognized representative viruses in the three genetic and antigenic groups quite well. And that was on the previous slide I showed you some of that -- or previous couple slides for the Victoria lineage.

But B/Yamagata, if we move to slide 55 now, group of viruses -- all these analyzed fell into clade three. We're seeing a nice homogenous genetic pattern there with not too much long branching. Most of the recent viruses are well-inhibited by ferret antisera against the current cell and egg propagated vaccine virus, B/Phuket/3073, and post-vaccination human sera to B/Phuket/3073-like antigens recognized representative viruses well.

The recommendation, we're going to move to slide 56 and then 57. Dr. Weir already covered this. I'll just hit it again quickly that there was a recommendation for the quadrivalent to contain Brisbane/2/2018. This represents a change for the

Southern Hemisphere from the Michigan/45, but it's the same recommendation as was made in the Northern Hemisphere earlier this year. The South Australia/34 was a recommended H3N2 virus.

I showed you data from this antigen with ferret antisera, both the cell and the egg pairs. So, this represents a new recommendation for the Southern Hemisphere, as well. It is in the 131K genetic group and a new recommendation for influenza B, so the B Washington/2/2019-like virus. This is this Victoria lineage group, and it's the triple deletion virus that I was describing. And both the egg and the cell pair cover those viruses very well. The B/Phuket/3073 is the B/Yamagata lineage recommendation. So that rec is unchanged. For the trivalent, it was recommended that they contain all the first three and lack the Phuket Yamagata lineage.

And then I'll end by really acknowledging all the WHO CCs: Beijing, Melbourne, London, Tokyo, and WHO Geneva staff, all the GISRS, University of Cambridge partners that you can see some of that cartography in

the large trees from, the Central Regulatory Laboratories. All our partners in the United States, particularly the Association for Public Health Laboratories, U.S. Air Force School of Aerospace Medicine, heavily known as USAFSAM. The Naval Health Research Center, our fitness forecasting partners in Europe and the United States and all of our staff here at the CDC. With a special thanks to Rebecca Kondor, Summer Galloway and Xiyan Xu, who really help with the creation of the data package that we use. Thank you.

DR. EL SAHLY: Thank you, Dr. Wentworth. H3N2 seemed still to be the story. The B/Victoria has changed to cover the triple deletion, although the serology seems to be reassuring even in the older vaccine. But predicting then the 2A1b would be the predominate one in the Southern Hemisphere going forward seems to be the major departure here.

I will begin with a question as the committee members also are coming through online for questions. Are we seeing, geographically, whole cocirculation within the same geographic location, the 2A1b and the

3A at the same time in any of these?

DR. WENTWORTH: Thank you for the question. Yes, as you surmised very well, the situation with the H3N2s remains to be quite dynamic, and the clade diversity at the global level is pretty dramatic. And that's what I tried to show you. The question was really are we seeing cocirculation of all these various subclades in certain regions. And the short answer is yes. I didn't get into some of this detail. But for example, in Europe, there's about equal number of viruses since February 1st until now.

So part of this is the data that we have, where we have strong numbers, really ends at the end of June and, in some cases, in July. So that's because of collection dates and by the time they're sequenced, all of that. So given that preface, since February 1st in Europe, there's been basically equally numbers of 2A1b 131K and 2A1b 135K and only a little bit less 3C3a viruses. In Central and South America, it was actually quite a similar pattern. So those viruses -- there they saw -- the majority of the viruses that they saw

in Central and South America were 3C3a, followed by 3C2a1b 135K viruses, followed by 2A1b 131K viruses. And then they did see some 2A2 viruses, which are the older viruses that are currently in the Southern Hemisphere vaccine.

So, in some regions -- in Africa, they saw quite a large distribution where they had 2A1b 135K viruses predominate, followed by 131K and almost equal with 3A viruses. And then they had some 2A3 viruses and a very small number of 2A2 viruses. So again, the 2A3 and 2A2 being kind of earlier viruses in an evolutionary sense and we're hoping will die. We don't want to have to worry about them anymore.

But really the major trend is there's cocirculation of 3A and the 2A1b viruses. Whether you pick the 131K flavor or the 135K flavor is different in different regions. And certainly the 3A, where it is cocirculating most heavily is in North America, South America and, to a lesser extent, in Europe and not really being seen in Asia or Oceana to any great extent. And finally, Oceana really saw only 131K

viruses.

DR. EL SAHLY: Mm-hmm. And within both regions, I know you may not have the answer to this, but extrapolating from our experience here, sometimes -- I think a couple years ago we had HvN2 prevalent in Texas by H1N1 across the border in Mexico. So even within these larger plots of lands really, is there, for example, predictability in certain populations, with the understand that this may not affect the recommendations when we're looking at the big view of this? But do we see that also at a smaller regional level, as well, or is that not something your group delves into?

DR. WENTWORTH: Well, we do look for it. The problem is we don't see it. There's not a -- sometimes, even within the United States, we can see regional differences between states. For example, we've seen Pennsylvania have a really wide array of cocirculating subclades; whereas, Georgia may have very dominate subclade. And it doesn't hold true year after year, so it seems to be very season dependent. And we

haven't found an age group that's so importantly predictive.

I think one of the things about the H3s in particular is they're cocirculating subclades typically have some distinction from each other and are almost equal in fitness, evolutionary fitness. So, it's hard to say which one would actually do better than another. What you can more easily say is that multiple groups will cocirculate. And that's partly why I spent a little bit of time on the Iowa/60 antigen because that represents a 131K virus at the base of the 131K group. However, it cross protects against basically all of the 2A viruses.

So, if you just make the 2A viruses a supergroup, you could say, really, there's only going to be 2A and 3A that circulate in the United States, for example, 3A being in our current vaccine and 2A viruses being a potential new and old emerging group. For example, the 2A1b 131K viruses actually circulated last season in the United States early in the season. But then we had really primarily H1N1 viruses at that

point in the season. But the H3s that we had were 2A1b 131Ks. However, they got completely displaced by the 3A viruses.

DR. EL SAHLY: Yeah. Okay. Thank you, Dr. Wentworth.

DR. WENTWORTH: So, part of the vaccine selection isn't just about what will circulate but what antigens will protect against wider groups, as well.

DR. EL SAHLY: Understood. Thank you. I would like to invite my committee colleagues if they have questions to Dr. Wentworth before we break.

DR. WHARTON: This is Melinda Wharton. Can I ask a question?

DR. EL SAHLY: Of course.

DR. WHARTON: Thanks. David, that was great. I know that the topic for our discussion today is the Southern Hemisphere strain selection. But having a change in the H3N2 as proposed by WHO at the beginning of the Northern Hemisphere influenza season does raise questions about what we're seeing now and to what degree we expect a good match with H3N2 with U.S.

circulating strains. I know this is a little off topic, but is that something you could comment on?

DR. WENTWORTH: Sure. I can comment on it. I think you know as well as I do we have a lot of trouble predicting what group of virus will be in our season, even at this stage. Right now, we don't have really any viruses that have come in early in October. The inter-seasonal viruses that we see over the summer are terrible predictors. We know that. A lot of those come in via travel to other locations and don't necessarily predict our season.

So as far as which group cocirculates, that's also not a great predictor. I think that we picked, for a vaccine for the Northern Hemisphere, the most antigenically distinct viruses circulating. So in the Northern Hemisphere, so U.S., Europe, and other locations in the Northern Hemisphere, we have seen repeated infections, national infections with 2A viruses, so that 2A supergroup. We've seen it since 2014 with Hongkong, that virus that was a vaccine antigen. So, it's been in three vaccines for the

Northern Hemisphere, the 2A viruses, so just small updates to the 2A viruses. Whereas human sera against the 2A viruses cross protects against virtually all those with quite equal levels. Where we saw the reductions with human sera was in 3A viruses. These reductions are even more striking between naïve ferrets.

So, one of the issues is the more antigenically distinct virus of the two potentials that are going to cocirculate, 3A viruses 2A and whatever flavor of 2A1 you want to get into, is the 3A. So, it represents a more antigenically distinct vaccine virus. Why it wouldn't be chosen for the Southern Hemisphere six months from now would be we aren't seeing a continued increase in that virus geographically. It hasn't really spread beyond South America.

So, it spread from North America into South America more, but the anticipation is, six months from now, will that continue to spread east? Or are the 131 and 135K viruses, this 2A group -- the supergroup 2A has been more successful than the 3A over the past five

years.

And then on top of that, the 131K vaccine virus cross reacting very well -- the cell version cross reacting with a lot of the circulating strains, whether or not they were older 2A1 viruses or the new 2A1b 135K or 2A1b 131K. So, I hope that addresses your question. I think the thing we can say pretty safely is we'll probably have a mixed season. We may not have much of an H3 season, which would be great, given that we've had quite a few H3 seasons recently.

DR. WHARTON: Okay. Thank you.

DR. MEISSNER: I'd like to ask you a question. First of all, thanks for that presentation. Enormous amount of data and you presented it very clearly. And I appreciate that.

DR. WENTWORTH: Thank you.

DR. MEISSNER: The question I have is you show quite a bit of data comparing the serologic response to cell vaccines versus egg-based vaccines. I guess it's important to present that to address the question of whether, when an influenza strain adapts to growth in

an egg, does that change some of the important antigenic characteristics. But have you -- it seems as though comparing the responses varies largely depending on the strain. But what's your personal thought about the, based on what you presented today, on the relative role of cell-based and egg-based vaccines?

DR. WENTWORTH: Oh, boy. So, I think that I did spend a bit of time on that, and there's two reasons for that. One I tried to allude to. In order to look at antigenic drift in a very specific way, the best-case scenario is to compare a cell antigen with the current viruses that are circulating. So, for example, one of the reasons we would update the vaccine is if there's enough significant antigenic drift to warrant the update.

And then the reason for comparing the egg version of it with those currently circulating viruses is a little different. It's not to look at antigenic drift because that may be misleading if we used an egg antigen to look for antigenic drift. But it's to look to determine if that egg antigen that was selected as a

vaccine candidate at one point in time is showing a greater reduction then it had when it was originally named as the vaccine candidate. You may recall, for example, the Singapore update was primarily to improve the egg vaccine and not necessarily because of antigenic drift that was significant. So, there's that piece.

Certainly, the cell antigens -- the jury's still out on how much the cell versus the egg matters because, of course, we haven't had a cell-based vaccine go into a lot of people until recently. So, there's that piece where we won't really know exactly until we have some more seasons under our belt. Certainly from a very hemagglutination inhibition or focus reduction assay, like a virus neutralization assay, the cell-based antigens have better breadth. They cross protect against more cocirculating variants better, and you would perceive that they would last longer as a vaccine virus in a more similar way to what you see with H1N1s or something like that. So, they do have this kind of better breadth.

Whether or not that translates when we get the right among of antigen in the vaccine and immunize people I think remains to be determined because a lot of -- I think one of the things people forget, because we get very focused in on this match, this optimal match, is that a lot of what the vaccine does is stimulate memory to either natural infection or prior vaccination. So, if an immunogen is really good at being a stimulating immunogen, it could be a very effective immunogen, regardless of it was recumbent in cell or egg. I'd invite Dr. Weir to comment if you want or other folks at FDA. There's a lot to it.

DR. WEIR: I can only add one thing. First of all, I thought your explanation was really good. But even the data that you presented today showed that, for example, the human serology data doesn't always distinguish egg and cell isolates in the same way that the ferret data does. And again, I think you alluded to this. The actual effectiveness of a vaccine may not always track with these differences either. So, it's just a very complex situation.

DR. MEISSNER: Can I ask you a follow up question, both of you? You said that you're using less hemagglutination inhibition assays and more neutralization. But isn't a neutralization titer more likely to reflect what happens in a human because it really includes not only HI but neuraminidase? It's more of a global assessment of vaccine responses. Is that not true?

DR. WENTWORTH: So, to a little bit of an extent that's true. But basically, if you HI, you neutralize. So, if an antibody is capable of HI-ing, it will neutralize because really what the HI is showing is it's blocking virus receptor interaction. Virus nudes really show the blocking of virus receptor interaction and, to a much more limited extent, maybe fusion of the virus particle with the cell. If done correctly, they NA shouldn't be a big part of this assay. But you may be right that some antibodies to NA can interfere in both cases, both the HI and the nudes. And we know that to be true when we get certain neuraminidase substitutions that occur when we

propagate the virus in vitro. So, we look very closely for those and don't use viruses like that in our assays because they kind of confound the data. But generally, they're very correlated, the virus nude and the hemagglutination inhibition. You could draw a line -- very correlated.

DR. MEISSNER: Thank you.

DR. WENTWORTH: You could think of virus neutralization, like you said, is a little bit broader way to define how well an antibody can block virus from getting into a cell. But the primary reason we use it for H3s is because they no longer bind the receptor efficiently, so then it's pretty darn easy to neutralize them when they don't bind. So, in the red blood cells that we have available to use that's part of the issue.

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

DR. MEISSNER: I have one more question. Could we go back to slide 12? Is that showing the structure of the hemagglutinin molecule on an A strain?

Is that what we're looking at there?

DR. WENTWORTH: Yeah. So, you're looking at the HA monomer, so solved by crystal structure. I should have explained this more. I apologize. The reason I show it here -- we look at it for all of them, for all the subtypes and lineages. But I just didn't -- for purposes of time, I didn't put it in all of them. Particularly when we don't see good differences by ferret antisera, it's nice to understand where the changes are in the molecule and even the particular amino acid substitution. Is it a more significant substitution or is it like a leucine to an isoleucine or something like that where it would be maybe less significant in a place that doesn't matter?

In this case, you're looking at the key differences that define this 6B1.A group, which are the S74R, the I295V, and the S164T. And then the 183 substitution is pointed out because it's right there up in the head where we do see a lot of immunodominance, more in humans than in ferrets, for example. And ferrets, as you can tell from the data, they don't

really recognize this change. But it's partly there to just illustrate that these substitutions are surface exposed. And they're in regions that we know are important to epitopes.

DR. MEISSNER: So, does that show us the stock as well as the head or it's only part of the HA molecule?

DR. WENTWORTH: No, it's the whole HA monomer, so it's showing the head and the stock. Sometimes you can see the stock color coded differently. In this particular case, we haven't. But if you look at the righthand side of that figure where at the base it says 6B1.A, right there, that very bottom amino acid that you can kind of point to, you can imagine a couple more amino acids below that. And then it would go into the viral membrane because that's peeled off when we do the crystal structure.

So, you don't see a little bit of the very bottom of the stock where it would attach to the virus and then go through the membrane. It even has a tail that goes into the inside of the particle. But then if

you follow that up to almost a little bit more than halfway, that's about where the head begins that you typically hear talked about.

DR. MEISSNER: Yup. And the question I had then is, when people talk about an improved influenza vaccine, the idea is that there may be a conserved epitope on the stock that's more constant or is conserved. The sequence is conserved. But it's clear there are still changes that occur in the stock, as well as the head.

DR. WENTWORTH: Yeah. That's correct. They tend to be more conserved because the stock has this function of being very involved in the fusion event, so it has to unfold at the right PH and create this six-helix bundle that then helps the virus fuse. So, it has this functional role that, when you start making substitutions in, could impact the PH of fusion, for example, which can be very important in how well the virus transmits amongst humans. So that's -- one of the reasons it's a good target is for that conservation. But it does change. If you look at the

stock from 1968 ‘til present, you’ll see amino acid substitutions in that region, even in the regions proposed to be great producers of stock antibodies.

DR. MEISSNER: Thanks.

DR. KURILLA: Yeah. David, if you could just go one slide ahead to 13, I just wanted to ask one sort of general question. So, it seems that when you’re making this decision of what the flu vaccine composition is going to be, it seems you’ve got two questions to address. The first is do we need to change? And then if we do need to change, what do we change to? So, if you look at the first question, is this the data, on slide 13, that you’re really making the decision that we need a different antigen in the mix because the one we used before is not covering the circulating strains? Is that a correct interpretation of how you used this data?

DR. WENTWORTH: Well, in some cases, that’s a correct inter -- in this particular case, it’s an incorrect interpretation because you can see, against the Michigan/45, 95 percent are reacting as like or the

lowest by any center being 87 percent reacting as like. So that would be considered a pretty good situation. It's just that we and others now appreciate very well that the ferret, when you immunize with an H1, really focus in in an immunodominant way to a region on the molecule that really isn't evolving in humans. So, it's in this region where I mentioned we call it the 153 to 157 corridor.

So, in that region of the hemagglutinin, the ferrets really -- any time you have a mutation there, ferrets will recognize that very well. It'll reduce the titer, and it wouldn't be considered like. And that's partly the reason why we spent more time with human sera and on things like what's the evolutionary pattern that we're seeing. For example, the 183P, all that parallel evolution where basically now 90 percent of the viruses have this amino acid substitution even though seven of them got there via a different route, a different evolutionary pathway.

DR. KURILLA: Are you saying slide 17, then, is where you're really saying, "Gee, we've really got

to think about a different immunizing antigen?"

DR. WENTWORTH: Yeah. In this case, slide 17 provides very powerful data illustrating that that 183P -- like if you just don't focus on all those individual viruses, if you can look at, say, for example, the second column, Michigan/45 egg and then the next column over, that's the very minimalist virus with the fewest changes from Michigan. But it does have that 183P, and you can see boom. There's a drop below the 50 percent geometric mean.

And it's much easier to see, generally, in the pediatric population because they haven't been exposed to so many H1s in their life. And most of what they've seen are Michigan/45-like or California/7-like viruses. So that combined with the genetics and other human sera data where we look specifically at individuals help drive the decision for H1s.

DR. KURILLA: Okay. Thanks.

DR. EL SAHLY: Okay. Hi, everyone. This is Hana again. So we will have another opportunity at discussing and asking questions after the break, during

which discussion, voting, and recommendations will be made. So we would like to have the break right now. This is scheduled for 45 minutes. So, we will reconvene at 1:00 p.m. Eastern Time. Thank you.

(BREAK)

OPEN PUBLIC HEARING

[NO REQUEST FROM THE PUBLIC]

DISCUSSION & RECOMMENDATIONS

DR. EL SAHLY: It is 1:00 p.m., so we can start with the roll call and then see if all of the members are back or not.

MS. HUNTER-THOMAS: Okay. Let me just confirm that the webcast is up and running again, and then we'll get started. Okay?

DR. EL SAHLY: Okay. Thank you.

MS. HUNTER-THOMAS: Thanks.

DR. BOLLINGER: Serina, this is Lisa Bollinger. We can see the webcast on our computers.

MS. HUNTER-THOMAS: Oh, thank you, Lisa. Thank you.

DR. SPEARMAN: Yeah, Serina. We can see it.

MS. HUNTER-THOMAS: Great. Great. Thank you. Okay, so, we'll go ahead and proceed with the roll call.

DR. EL SAHLY: Okay. Welcome back, everyone. Dr. Hayley Gans?

DR. GANS: Here.

DR. EL SAHLY: Dr. Holly Janes?

DR. JANES: I'm here.

DR. EL SAHLY: Dr. Michael Kurilla?

DR. KURILLA: Here.

DR. EL SAHLY: Dr. Cody Meissner?

DR. MEISSNER: I'm here.

DR. EL SAHLY: Dr. Paul Spearman?

DR. SPEARMAN: Yes, I'm here.

DR. EL SAHLY: Dr. Geeta Swamy?

DR. SWAMY: Here.

DR. EL SAHLY: Mr. Sheldon Toubman?

MR. TOUBMAN: Here.

DR. EL SAHLY: Dr. Melinda Wharton?

DR. WHARTON: Here.

DR. EL SAHLY: Dr. Tammy Beckham?

DR. BECKHAM: Here.

DR. EL SAHLY: Dr. Steven Pergam?

DR. PERGAM: I'm here.

MS. HUNTER-THOMAS: And Hana, if I could request real quick, Dr. Pergam wasn't with us this morning. So, if he can do a quick introduction and association of his affiliation for the benefit of the group.

DR. EL SAHLY: Yeah, that's fine.

DR. PERGAM: Sure, I'm happy to do that. I'm Steve Pergam. I'm an associate member at Fred Hutchinson Cancer Research Center and an associate professor at University of Washington. I serve as the Infection Prevention Director at the Seattle Cancer Care Alliance here, so I'm really looking forward to looking to working as a group.

MS. HUNTER-THOMAS: Thank you, Dr. Pergam. If you will, Dr. El Sahly, I just want to check and make sure that I heard Lisa Bollinger; Dr. Bollinger is on because she confirmed the webcast. And Dr. Wentworth, he's on.

DR. WENTWORTH: Yes, I'm here.

MS. HUNTER-THOMAS: Okay. Perfect. Okay. Handing it back to you, Dr. El Sahly. Thanks.

DR. EL SAHLY: Okay. Thank you all for returning to the call. This morning, we heard an extensive presentation of the genetic and antigenic diversification of the various flu strains from a global perspective in an attempt to vote on the selection of the flu strains for the Southern Hemisphere flu vaccine. We heard a few questions from a few committee members earlier today, and I would like to begin by inviting the committee members to ask additional questions or provide additional comments.

DR. SPEARMAN: Hi, this is Paul Spearman. I was hoping to ask one. Thank you for that really interesting and complex picture and analysis that is

done on the flu strains.

What I'd like to know, maybe in helping understand this process in the future, when you look at the geographic distribution, or instance, (phone audio cuts out) -- very geographic distribution, do you look back over time as to how these clades are evolving in geographic space and use that in any way to help with strain selection? Or is it purely based on the most recent identified strains that you very carefully described to us and their antigenic specificities?

DR. WENTWORTH: Thank you for the question. In general, one of the things the CDC does is we do look back in time. We're constantly looking for some kind of cues that would help forecast with fitness forecasting better. Just to get directly to the strain selection process, we don't discuss that very much during the strain selection process. Part of the rationale of that is that we don't see patterns.

I can give you a specific example. A lot of people like to use Australia to say well that would predict what happens in North America, right? But

Australia has a very good surveillance system, and this is one of the reasons why we like the data, right? But on the other hand, the past three seasons, the clade that predominated in Australia didn't predominate in the U.S. in H3, for example, where we have the most clade dynamics happening.

So, that doesn't work. And then if you take whole regions as a whole, you can kind of overgeneralize and say, well, Southeast Asia and Oceana kind of help forecast us or Northern hemisphere, and the Northern hemisphere helps to forecast the Southern hemisphere. But within H3N2 we don't see specific trends. We are drilling into it in a lot of different aspects using different statistical approaches to try to understand this.

But that's as far as I can tell you. We're not seeing the trends; we do look for them. And I think there was a question about age group earlier. We're trying to slice the data by age group as well to see if there would be maybe an age group and a region that would help to give you an idea of the virus that

would be the most fit.

DR. SPEARMAN: But the dominant strains in the Southern hemisphere that we're seeing aren't necessarily what we're going to be seeing in the Northern hemisphere in the next season. Is that right?

DR. WENTWORTH: Well, I think when you say the entire Southern hemisphere, you couldn't be correct. Right? Because, as I showed you in the geographic overlay, in South America, we see a lot of 3C3A viruses. And we don't see very many 3C3A viruses in Oceana, for example. So, I think it's more regional than a Southern and a Northern hemisphere, right? There's more human back and forth and more goods back and forth the closer people are together. So, some of it's, I think, that.

The question really for us, in the Northern hemisphere and in North America, is will we see what's in South America push back up to North America as the season progresses? In which case we would have quite a bit of 3A because that was their predominant virus. But it could be that we were ahead of South America

last year and the virus that we had moved south, right? So, you have both of those things happening.

DR. SPEARMAN: Thank you. That's even more complex than I thought.

DR. BOLLINGER: This is Lisa Bollinger. Can I just ask one question about predicting the way that the virus is going to spread and potential strains that we would target? And that is, in today's big data and AI, is there any possibility to put the historical data into some sort of model that would allow us to predict the strains for the coming years?

DR. WENTWORTH: Well, yeah. This is done by quite a few predictive modeling groups. We work, for example, very closely with Trevor Bedford and Richard Neher around the Nextstrain, Nextflu site. They are contributing to the vaccine consultation meeting now on a regular basis, as well as another group led by Martha and Michael -- I'm blanking on his last name. But that group as well.

What happens is, just to answer your question more specifically, when you build a model based on

historical data, you can predict correctly that historical data. For example, you predict the emergence of 3C2A viruses in 2014-15 season. So, you build this model that can predict that based on all the historical data and it does that well. But as soon as you go into the out years where there wasn't training data for it, it doesn't do very well. So, there's a lot of groups working on this. It's just that the models really aren't very predictive.

DR. BOLLINGER: Thank you.

DR. PERGAM: David, this is Steve in Seattle. Just a question, I know there's some emerging interest in looking at the neuraminidase antibodies. Is there any work that's being done to sort of use these as secondary evaluations in terms of vaccine efficacy?

DR. WENTWORTH: Okay. Yes. There are multiple approaches. For the NA, I really didn't spend much time on the NA here because we weren't seeing huge changes in the NA. They were pretty similar, so I just left it out. But we are always looking at the NA. We look at it more now than we have in the past. In fact,

members of the FDA specifically look at the -- so we look at the evolution of the NA and then we also look at the antigenicity of the NA. Antigenic analysis of NA is actually more complicated than antigenic analysis of the HA.

A team in the FDA, led by Zhiping Ye, actually looked specifically at the antigenicity of the NA and they didn't see evidence of drift in this particular case. With regards to VE, it's even more complicated as to how the NA will impact the vaccine estimates. Because typically, the vaccine virus -- you'd have to look for an area where you have two different vaccine viruses, one with a different NA than the other.

So, right now, for example, the biggest substitution in the NA was at position 245. This added a glycosylation site that looks like it really impacts antigenicity. That is virtually in all of the neuraminidases now circulating, even the neuraminidases in the 3C3A group and the neuraminidases in the 3C2A group.

DR. PERGAM: I appreciate that.

DR. JANES: Dr. Wentworth, this is Holly Janes in Seattle. I think I saw in the WHO summary and recommendation document that there's been some in vitro testing of susceptibility of the circulating viruses to existing antivirals. And if that's so, can you kind of summarize what's known there, I guess more broadly on efforts to collect clinical outcomes associated with the circulating viruses?

DR. WENTWORTH: Yeah. I was contemplating whether to include all the antiviral stuff in this presentation. But I'm going to just summarize it very briefly. We saw very few viruses that were resistant or were not susceptible to the antivirals. We did document it in the WHO recommendation as to how many in each group -- the H1, the H3, the Bs. So, for specific data, I really urge you to go there. I don't have it handy. It's just a very small percentage. We're not seeing any trends of any increasing neuraminidase resistance.

We also are now looking at Baloxavir sensitivity by two methods. One, sequence analysis

within the five-prime end of the gene or the amino terminal end of the protein, to look specifically for mutations. One of the classic mutations is at position 38 with a PA. So, we look that way. And then we also take anything that has substitutions there and do phenotypic testing. Here at the CDC we're doing that, and at the Japan collaborating center they are also looking at that.

So, all of that is being done concomitantly with the antigenic analysis that's ongoing. If you had a specific question, I can certainly address it.

DR. JANES: Great. That's great to hear. Are there ongoing efforts to assess whether there are any differences in morbidity associated with the various circulating viruses? I don't remember that we've been shown data to that effect. Is that on ongoing expanding efforts?

DR. WENTWORTH: Yeah. So, we do track, here at the CDC and at the other collaborating centers, a couple of different things. There are some studies that are more based in SARI surveillance, so more

severe disease surveillance. So, there are specific sites around the world where SARI is one of the primary ways that they get their samples in.

And then, in the United States, which I can speak more definitively about because I know all the data very closely, in the specimen submission form, we're requesting mostly -- you know, anytime there's a fatal outcome we usually get that virus in, for example. We also know whether or not there's hospitalization or fatal outcomes in most of our surveillance, as well as most of it comes through non-severe outcomes. So, through just typical clinical presentations.

But we do know those particular cases where they have resulted in fatalities and severe disease. So we're always looking at those to see if there's any sort of grouping genetically. And of course, it's easiest for us to see in the hemagglutinin because we spend an awful lot of time there. But now we do complete genome sequencing on almost all of the viruses that come in.

So, we do, over time, look for associations with the other genetic components as well. But typically, it's rare to see a smoking gun in the virus because humans are so different from each other. Often, we'll see nearly identical viruses in a severe case as we do in a non-severe case.

DR. JANES: Um-hm. Okay. Thank you.

DR. KURILLA: David, your analysis is based, it seems, exclusively on humoral immunity and even a subset of that, because you're really not evaluating something like ADCC.

DR. WENTWORTH: Correct.

DR. KURILLA: So, the question is, is this the approach because you don't feel cell-mediated immunity is as important, or that it's technically just beyond your capability to evaluate?

MS. HUNTER-THOMAS: Who was that that was speaking? Sorry.

DR. KURILLA: Mike Kurilla. Sorry.

MS. HUNTER-THOMAS: Thanks.

DR. WENTWORTH: Well, I think it's

multifaceted is the answer to that. Historically, we know that neutralizing the virus from infecting is a great way to protect people. So, a good neutralizing titer is a correlate of protection.

With T cells, certainly we want to begin to evaluate more their impact. It's not really beyond our capability to evaluate; you wouldn't be able to evaluate it, I think, at the level that we evaluate antigenicity, like, the numbers. But because of all the genomics being conducted, you could identify subsets and do more T cell work based on those subsets. Right?

So, this is certainly an area, and it may be necessary, depending upon the types of vaccines that we make in the future. But currently, the biggest correlate is good neutralizing titers. And it is a light you can shine on many viruses, so to speak, with a higher throughput approach, right?

But if it comes to T cells, just for example, the 3C3A virus and the 3C2A viruses that we were just describing, those two vaccine viruses are nearly

identical in their hemagglutinin. Really, they have very few amino acid substitutions. So, when you think about how that hemagglutinin would be broken up and presented by T cells, most of it would be the same whether it was 3C3A or 3C2A.

DR. KURILLA: Thanks.

DR. EL SAHLY: Any additional comments?

DR. BOLLINGER: This is Lisa Bollinger. Can I just ask one more quick question? That is, when we look at the data on immunogenicity across the population, do we ever select strains based on the importance of certain patient subgroups as far as vulnerability to influenza -- like worst disease -- such as pediatric patients or the elderly? Or do we go for the mean of the population?

DR. WENTWORTH: Okay. We always consider those impacted by the disease more severely, and the pediatric and elderly are those. But it's not a direct -- it's not like, oh, we have to protect this group at the expense of another group. Right?

But as an example, with the H1N1s that I

provided, in part, it could happen indirectly because in a pediatric population they haven't been exposed to many viruses throughout their lifetime. So, it's easier with sera from that population to identify small differences between related viruses, right?

And it is very much considered in influenza B viruses and in Victoria where they can impact kids. And one of the -- you know, can be a driver for change as well. It's always a collective decision. It's not any one thing. I really hope that comes across.

We take into account vaccine effectiveness, which we haven't even discussed today. But how well is the current vaccine working in the most recent season? And are there signals there? Or are there signals in specific age groups in VE that we can identify? And that has been identified in the past, particularly for H1N1 viruses. They weren't the pediatric population in that case.

So, the long answer is kind of the long answer. The short answer is, yes, the specific groups are thought about and in part, also, when it comes to

the trivalent and quadrivalent as well.

DR. WENTWORTH: So, what we conclude in a trivalent would be the new antigenic virus because that, if it's going into a pediatric population, they've never seen that virus before.

DR. BOLLINGER: Thank you.

DR. GRUBER: So, can I make a comment -- this is Marion Gruber -- along the lines or just to add on what was just discussed. And that is, are we really looking at immune status or certain subpopulations when we're looking at making vaccines available? I just wanted to point out, there are influenza vaccines that we have licensed where we really have the immune status of the population in mind.

For example, a couple of years ago we licensed Fluzone High-Dose. Where we basically adjusted the dose of the concentration of the influenza vaccine antigens to be administered to the elderly, because there's recognition that, because of immunosenescence and other factors, the elderly may not respond as well. So, there are efforts being made to also tailor certain

vaccine products to these types of subpopulations. Thank you.

DR. GANS: Hi. This is Hayley Gans. I had a quick question. Most of my questions have been answered. But I had a question about the different strains' activity and the different vaccine formulations. We seem to be concentrating mostly on the injectable but obviously there's the live viral nasal formulations. And while they carry the same strains, is there any -- and I haven't seen this variability and what does well in one formulation versus another, and should that be considered at all? I guess that's the question, strain specific.

DR. WENTWORTH: I think, as far as the product variability, I would rather turn it over to FDA. But the short answer is, with the LAIVs, we basically are trying to match the recommended strains. The LAIV companies submit the strain that they are planning to use for two-way antigenic testing to one of the collaborating centers that has the recommended strain, or the like recommended strain. And then it passes

that and then can be moved -- and then they submit to FDA for potency and things like that.

DR. EL SAHLY: Dr. Weir, would you like to weigh in on the matter?

DR. WEIR: Yes. I can add just a little bit. First of all, this doesn't apply to the Southern hemisphere formulation for us in the U.S. But the process for selecting the strains, the WHO recommendation does apply. And actually, our VRBPAC recommendation for the Northern hemisphere does apply to the inactivated vaccines as well as live attenuated vaccines.

So, yes, the maker of a live attenuated vaccine also has to formulate a vaccine that meets those recommendations. It is true that, over the last few years, there has been an increase in the amount of data that comes out as to the effectiveness of vaccines. In recent years, there has been enough data to actually distinguish the effectiveness of inactivated vaccines sort of as a broad class -- all of them lumped together, not necessarily manufacturer

specific -- and distinguish those between the effectiveness of live attenuated vaccines.

That's happened over the last few years, and you see varying degrees of effectiveness depending on the year. But I don't know that I can say much more about it than that.

DR. GANS: Great. Thanks.

DR. EL SAHLY: And there's always the added complexity in this big set of data that we've used today. And predicting the effectiveness or efficacy of the LAIV is not as correlated with the HAI and responses as the other two vaccines, certainly not perfectly. Any additional comments?

I would like to point out here one thing in that Captain Serina Hunter-Thomas did confirm that there are no requests from the public. So, that's why we did not read the open public hearing statement. I would like to turn maybe the slides to the recommended strains so we can take a final roll call with comments, and then voting.

MS. HUNTER-THOMAS: Dr. El Sahly, you want the

questions slide shown?

DR. EL SAHLY: Yes, please.

MS. HUNTER-THOMAS: Okay. There you go.

DR. EL SAHLY: All right. So, we will go over the room just to make sure that everyone's questions have been answered satisfactorily to the limits of what's norm, at least. Dr. Hayley Gans?

DR. GANS: Nothing.

DR. EL SAHLY: Dr. Holly Janes?

DR. JANES: Nothing further for me.

DR. EL SAHLY: Dr. Michael Kurilla?

DR. KURILLA: No further comments or questions.

DR. EL SAHLY: Dr. Cody Meissner?

DR. MEISSNER: No more questions.

DR. EL SAHLY: Dr. Paul Spearman?

DR. SPEARMAN: Nothing further. Thanks.

DR. EL SAHLY: Dr. Geeta Swamy?

DR. SWAMY: Nothing further.

DR. EL SAHLY: Mr. Sheldon Toubman?

MR. TOUBMAN: No, thank you.

DR. EL SAHLY: Dr. Melinda Wharton?

DR. WHARTON: No additional questions. Thank you.

DR. EL SAHLY: Dr. Tammy Beckham?

DR. BECKHAM: No questions. Thank you.

DR. EL SAHLY: Dr. Steven Pergam?

DR. PERGAM: I have no further questions. Thanks.

DR. EL SAHLY: Dr. Lisa Bollinger?

DR. BOLLINGER: No further questions. Thank you.

DR. EL SAHLY: Any final remarks from Dr. Wentworth? I know that you've been put on the spot all day long, but --

DR. WENTWORTH: No. No more comments from me. I would mention that the other person that contributes fitness forecasting data is Michael Lassig's team.

VOTE (TOPIC II)

DR. EL SAHLY: Okay. All right. So, we have

the questions on the screen. I'm going to read them out loud and then, per Serina's instructions, again, we should be sending accept, reject, or accept with changes. Is that correct, Serina?

MS. HUNTER-THOMAS: Almost. So, for these two questions, the options are yes, no, or abstain.

DR. EL SAHLY: Oh. Yes, no, abstain. Yes. That's the second row. Sorry.

MS. HUNTER-THOMAS: Okay.

DR. EL SAHLY: Okay. The questions. Question one: For the composition of trivalent 2020 Southern hemisphere formulations of influenza vaccines, does the committee recommend inclusion of an A/Brisbane/02/2018(H1N1)pdm09-like virus, inclusion of an A/South Australia/34/2019(H3N2)-like virus, inclusion of a B/Washington/02/2019-like virus Victoria lineage? Please send your vote to Serina via email. Dr. Gruber would like to make a comment. Please, go ahead, Dr. Gruber.

MS. HUNTER-THOMAS: Not right -- before we adjourn, after the voting.

DR. EL SAHLY: Oh, after the voting.

MS. HUNTER-THOMAS: Yes. Sorry. Thank you. I wasn't clear. Thank you. Okay, we're almost there. I just received yours, Dr. El Sahly. And Dr. Pergam, I just received yours. Okay. So, I will read aloud for the record the voting results for question number one. And just to clarify, some folks have already voted for question number two, but I need to get that separately, okay?

The voting results for question number one, starting with Dr. El Sahly, is a yes. Dr. Gans is a yes. Dr. Janes is a yes. Dr. Kurilla, yes. Dr. Meissner, yes. Dr. Spearman, yes. Dr. Swamy, yes. Mr. Toubman, yes. Dr. Wharton, yes. Dr. Beckham, yes. And Dr. Pergam, yes. Is that confirmed for everyone?

DR. MEISSNER: Yes.

DR. EL SAHLY: Yes.

MS. HUNTER-THOMAS: Okay. And the results are now posted for the benefit of everyone on the webcast. Dr. El Sahly, are we ready to proceed to question number two?

DR. EL SAHLY: Let's do that.

MS. HUNTER-THOMAS: Okay.

DR. EL SAHLY: Okay. Question number two for voting: For the quadrivalent 2020 Southern hemisphere correlation influenza vaccine, does the committee recommend inclusion of a B/Phuket/3073/2013-like virus, Yamagata lineage, as the second influenza B strain in the vaccine? Please send your vote to Serina via email.

DR. PERGAM: Do we need to resend it?

MS. HUNTER-THOMAS: Yes please. Thanks. Okay, we just have one more pending and that is Dr. Gans.

DR. GANS: I sent you mine. Should I send it again?

MS. HUNTER-THOMAS: Okay. I'm sure it's just waiting to push through, I guess.

DR. GANS: I sent it a while ago. I'll resend it.

MS. HUNTER-THOMAS: Okay. I see it now. Thank you. Okay. So, all the votes are in for

question number 2. And for the benefit of the record, I'll read aloud. Starting with Dr. El Sahly, the response is yes. Dr. Gans, yes. Dr. Janes, yes. Dr. Kurilla, yes. Dr. Meissner, yes. Dr. Spearman, yes. Dr. Swamy, yes. Mr. Toubman, yes. Dr. Wharton, yes. Dr. Beckham, yes. And Dr. Pergam, yes.

DR. EL SAHLY: Okay. Dr. Marion Gruber?

MS. HUNTER-THOMAS: And the results for question number two are on the screen. Thank you. Dr. Gruber?

DR. GRUBER: Yes. Thank you very much. What I wanted to do is actually, first of all, thank the committee for their discussion, their recommendation and their vote. We know that these discussions regarding flu strain selection are always complex and very complicated. So, your efforts and help in that regard are much appreciated.

But I also wanted to take a moment here to express my appreciation and thank Captain Serina Hunter-Thomas for an exemplary job that she has done over the last couple of years and providing her support

in the planning, organizing, and conducting our advisory committee meetings. We really could not have done it without her help and support.

Regretfully, Serina is moving on. This is her last meeting of the Vaccines and Related Biologic Products Advisory Committee. So, I just want to take a moment, Serina, to really thank you from the bottom of my heart for all the work that you have done, for your creativity and really jumping in the last minute and helping us out. When we thought a committee meeting could not happen because of X, Y, and Z, you were there, and you helped us. So, on behalf of the Office of Vaccines, thank you very much and we wish you well. Thank you.

MS. HUNTER-THOMAS: Thank you, Dr. Gruber.

DR. EL SAHLY: I will miss you, personally, Serina.

MS. HUNTER-THOMAS: Yeah. Sorry I didn't get a chance to send out the memo. We've been so busy.

DR. EL SAHLY: Well, wishing you good luck on whatever endeavor you take on next.

MS. HUNTER-THOMAS: Thank you. Thank you so much. Without further ado, I think, Dr. El Sahly, are we able to adjourn?

DR. EL SAHLY: Okay. Yes. Definitely. Thank you all for participating. The meeting is adjourned.

MS. HUNTER-THOMAS: Thank you, everyone. Have a great day.

DR. EL SAHLY: Thank you, everyone. Bye-bye.

[MEETING ADJOURNED FOR THE DAY]