FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)

153rd Meeting of the Vaccines and Related Biological Products Advisory Committee

FDA White Oak Campus
Building 31, Great Room Salon B & C
Silver Spring, MD

October 3, 2018

PARTICIPANTS

Kathryn Edwards, M.D.	Vanderbilt University School of Medicine
David Greenberg, M.D.	Sanofi Pasteur
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
Michael Kurilla, M.D., Ph.D.	National Health Institute
Myron Levine, M.D., D.T.P.H., F.A.A.P.	University of Maryland
Arnold Monto, M.D.	University of Michigan
Ofer Levy, M.D., Ph.D.	Boston Children's Hospital
Paul Offit, M.D.	The Children's Hospital of Philadelphia
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Spearman, M.D.	Cincinnati Children's Hospital
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine
Sheldon Toubman, J.D.	New Haven Legal Assistance Association
Geeta K. Swamy, M.D.	Duke University
Melinda Wharton, M.D., M.P.H.	National Center for Immunization and Respiratory Disease
Jacqueline Katz, Ph.D	National Center for Immunization and Respiratory Disease
Marion Gruber, Ph.D.	Food and Drug Administration (FDA)
Jerry P. Weir, Ph.D.	Food and Drug Administration (FDA)
Philip Krause, M.D.	Food and Drug Administration (FDA)
Zhiping Ye, M.D. Ph.D.	Food and Drug Administration (FDA)
Serina A. Hunter-Thomas, M.S.A., R.N.	Food and Drug Administration (FDA)
Joanne Lipkind, M.S.	Food and Drug Administration (FDA)
Prabhakara Atreya, Ph.D.	Food and Drug Administration (FDA)

TABLE OF CONTENT

OPENING REMARKS/CALL TO ORDER/INTRODUCTIONS

MS. EDWARDS: This Is Kathy Edwards. I'm very pleased to welcome you to the Strain Selection Meeting for the 2018 Southern Hemisphere Influenza Season. I would particularly like to welcome our newest members, Dr. Kurilla, Dr. Meissner and Dr. Swamy. This is their first meeting and we all are very pleased to have you with us.

I would like to go though the member list. Just say your name and then please tell us where you're from and your area of expertise.

I'm Kathy Edwards. I'm pediatric infectious disease and the chair of the committee from Vanderbilt University. David Greenberg, can you give us your information?

DR. GREENBERG: Yes. David Greenberg, pediatric infectious diseases, Sanofi Pasteur, the industry representative.

DR. EDWARDS: Thank you, David. Holly Janes?

DR. JANES: Good morning. This is Holly Janes. I'm a biostatistician. I work at the Fred Hutch in vaccine evaluation and clinical trial science.

DR. EDWARDS: Thank you. Lenny Friedland?

MS. HUNTER-THOMAS: Not here for this meeting, Dr. Edwards.

DR. EDWARDS: Michael Kurilla?

DR. KURILLA: Mike Kurilla from National Institutes of Health. I'm currently with the National Center for Advancing Translational Sciences, formerly with the National Institute of Allergy and Infectious Diseases. I'm a pathologist by training, specialized in infectious diseases and vaccine development.

DR. EDWARDS: Wonderful. We welcome you greatly. Dr. Monto?

DR. MONTO: Arnold Monto. I'm in epidemiology at the University of Michigan, School of Public Health. I work in influenza and other respiratory viruses.

DR. EDWARDS: Thank you. Ofer Levy.

DR. LEVY: Hello, this is Ofer Levy. I'm a physician scientist at Boston Children's Hospital where I attend on the pediatric infectious diseases service. I'm a professor at Harvard Medical School in pediatrics. I also direct the Precision Vaccines Program at Boston Children's Hospital, which is a platform to encourage collaboration of academia, government and industry towards developing vaccines to vulnerable population.

DR. EDWARDS: Thank you, Ofer. Cody Meissner.

DR. MEISSNER: Yes, I'm a professor of pediatrics at Tufts University School of Medicine. I have had an interest in various vaccines for a number of years.

DR. EDWARDS: Thank you and welcome, Cody. Paul Offit?

DR. OFFIT: Yes, I'm a professor of pediatrics in the Division of Infectious Diseases at Children's Hospital of Philadelphia, and a professor at the University of Pennsylvania School Of Medicine.

DR. EDWARDS: Thank you, Paul. Paul Spearman?

DR. SPEARMAN: Hi, this is Paul Spearman. I'm division director at Cincinnati Children's for Pediatric Infectious Diseases. I'm an HIV virologist and also work on other viruses and work closely with our vaccine trials unit on clinical trials for many vaccines.

DR. EDWARDS: Thank you, Paul. Andy Shane?

DR. SHANE: Hi, good morning. I am Andy Shane. I'm an associate professor of pediatrics at Emory University in Atlanta and the interim division director. I'm also the hospital epidemiologist. I have a long-standing interest in vaccines. Thank you.

DR. EDWARDS: Thank you. Geeta Swamy? Welcome, Geeta.

DR. SWAMY: Thank you, good morning. I am a faculty member at Duke University in obstetrics and gynecology in maternal-fetal medicine. My area of interest is in maternal immunization and women's immunizations across the board for adult diseases as well.

DR. EDWARDS: Thank you, Geeta. Sheldon

Toubman?

DR. TOUBMAN: Good morning. I'm an attorney with New Haven Legal Assistance Association in New Haven, Connecticut. My area is health law and particularly Medicaid law. I have no technical background, which is why I'm actually the consumer representative for this committee.

DR. EDWARDS: Thank you. Melinda Wharton?

DR. WHARTON: Hi, I'm an adults' infectious disease physician and I'm director of the immunization services division at the Centers for Disease Control and Prevention in Atlanta.

DR. EDWARDS: Thank you, Melinda. Tammy Beckham? Serina, she will not be able to join us, is that correct?

MS. HUNTER-THOMAS: That is correct.

DR. EDWARDS: Okay, great. Have I forgotten anybody? I will introduce the speakers, and would you like to introduce the FDA participants please? Introduce themselves.

DR. GRUBER: Hello, my name is Marion Gruber.

I'm the director of the Office of Vaccines, Research and Review at CBER.

DR. EDWARDS: Thank you, Marion.

DR. WEIR: And this is Jerry Weir. I'm the director of the Division of Viral Products at CBER.

MS. HUNTER-THOMAS: And we also have Dr. Prabhakara Atreya who is the director of Division of Scientific Advisors and Consultants. And I am Serina Hunter-Thomas, the Designated Federal Officer for this advisory committee. Thank you.

DR. EDWARDS: Thank you. Serina, would you like to read the housekeeping and conflict of interest now that we have had our call to order and introduction of the committee members?

MS. HUNTER-THOMAS: Sure. First though, I would like to check and see if Dr. Jacqueline Katz is on the line. Jackie?

DR. KATZ: Yes, hi, Serina, I'm here.

MS. HUNTER-THOMAS: Hi. Good morning. Would you like to introduce yourself before I go on with housekeeping?

DR. KATZ: Sure. I am the deputy director of the Influenza Division here at the CDC. And I'm also the director of the WHO Collaborating Center in Atlanta at the CDC for influenza.

MS. HUNTER-THOMAS: Thank you. Dr. Edwards, if I may, I'll proceed with the housekeeping and the conflict of interest statement.

DR. EDWARDS: Please, thank you so much.

ANNOUNCEMENTS, CONFLICT OF INTEREST STATEMENT

MS. HUNTER-THOMAS: Thank you. Good morning again everyone. My name is Serina Hunter-Thomas. I'm the Designated Federal Officer for the 153rd VRBPAC meeting.

The committee management specialist for this meeting is Ms. Joanne Lipkind and the committee management officer for this meeting is Ms. Casey Stewart.

On behalf of the FDA, the Center for Biologics Evaluation and Research, and VRBPAC, we would like to

welcome everyone to this meeting.

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the federal register notice that was published on August 16, 2018. The press media representative for today's meeting is Ms. Megan McSeveney. The transcriptionist for this meeting today is Ms. Linda Giles.

I would like to remind everyone to please first state your name when you are speaking and making a comment and project, because all of the committee members are joining us remotely today. I will now proceed with the conflict of interest statement.

The Food and Drug Administration is convening today, October 3, 2018, for the 153rd meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of Federal Advisory Committee Act of 1972. The entire meeting will be conducted in open session, during which the committee will discuss and make recommendations on the selection of strains to be included in an influenza virus

vaccine for the 2019 Southern Hemisphere influenza season.

This topic is determined to be a particular matter involving specific parties. With the exception of the industry representative, all participants of the committee are special government employees or regular federal government employees, from other agencies, and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this advisory committee's compliance with Federal Ethics and Conflict of Interest laws, including but not limited to, 18 U.S. Code § 208, is being provided to participants at this meeting and to the public. This conflict of interest statement will be available for public viewing at the registration table.

Related to the discussions at this meeting, all members and consultants of this committee have been screened for potential financial conflict of interests of their own, as well as those imputed to them, including those of their spouse or minor

children, and for the purposes for 18 U.S. Code § 208, their employers.

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

Under 18 U.S. Code § 208, Congress has authorized 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. David Greenberg is currently serving as

the industry representative to this committee. Dr. Greenberg is employed by Sanofi Pasteur. 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 are 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 appointed special government employees and are screened and cleared prior to their participation to 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. Jacqueline Katz is employed by the Centers for Disease Control and Prevention, Nation Center for Immunization and Respiratory Diseases. She is an

expert in influenza virus disease and influenza virus vaccines, and internationally known for these achievements. Dr. Katz is a regular government employee and serves as the speaker for this meeting. She is not a voting member for this committee.

At this meeting there may be regulated industry speakers and others outside organization speakers making presentations. These participants may have financial interests associated with their employer and with other regulated firms. The FDA asks that in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

The 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 concludes my reading of the conflicts of interest statement for the public record and at this time I would like to turn the meeting back over to Dr. Edwards, the Chair. Thank you.

DR. EDWARDS: Thank you so much, Serina. We would now like to introduce Dr. Jerry Weir who will introduce and present the questions that we will be addressing today. Dr. Weir is the director of the Division of Viral Products at the Office of Vaccines Research and Review at CBER/FDA.

INTRODUCTION AND PRESENTATION OF QUESTIONS

DR. WEIR: Thank you. I'm going to provide a brief introduction and a little background, especially for those of you who are new to this process. Then as

Dr. Edwards said, I'll present the questions at the very end. If we can go to the next slide, the second slide?

The purpose of today's VRBPAC Committee discussion is to make recommendations for the strains of influenza A (H1N1 and H3N2) and the B viruses to be included in the 2019 Southern Hemisphere formulation of influenza vaccine licensed in the United States. The next slide?

As a little bit of background, the World Health Organization makes recommendations for the virus strains to be included in influenza vaccines two times a year. The recommendations for the Northern Hemisphere are made in February or March, and the recommendations for the Southern Hemisphere are made in September.

Even though the WHO makes these recommendations, each national regulatory authority must approve the composition and formulation of vaccines in each country. For us in the United States, this committee, the VRBPAC, provides

recommendations for US licensed vaccines. In February or March, we do this for vaccines to be used in the Northern Hemisphere influenza season. This is for us, the US influenza season.

The FDA/CBER approves the licensed supplements for each manufacturer to incorporate updated strain recommendations. For the Northern Hemisphere we usually do this in June or July preceding the influenza season. However, in 2016, a US vaccine manufacturer was approved to produce a Southern Hemisphere formulation of their influenza vaccine. This is an egg-based vaccine.

We feel that it's important that strain recommendations and supplement approval for the Southern Hemisphere formulations for anyone in the US -- any US manufacturer -- follow the same Northern Hemisphere process. That being said, our process and what we do today in the VRBPAC is a somewhat streamlined version of what we do in February or March for the real Northern Hemisphere season. Go to the next slide.

What you will hear in Dr. Katz's presentation will be several different types of data and analyses. They will include the epidemiology of circulating strains, surveillance data from both the US and around the world. This is summarized from the most recent WHO Southern Hemisphere strain selection consultation which occurred last week.

You'll also hear about antigenic relationships among contemporary viruses and candidate vaccine strains. This will include data such as hemagglutination inhibition and virus neutralization tests. Also, HI and virus neutralization tests using panels of sera from humans whom have received recent inactivated influenza vaccines. And you'll probably see some data on antigenic cartography, as well as phylogenetic analyses of HA -- hemagglutinin and neuraminidase genes. Next slide.

In the next three slides I'm going to briefly review what we've done in the strain selection meetings of VRBPAC over the last year. About a year ago, in September, the WHO made a recommendation for

the Southern Hemisphere 2018. At that time the WHO recommended that the following viruses be used for a trivalent influenza formulation. They recommendation an A/Michigan/45/2015 pandemic 2009-like virus, an A/Singapore/INFIMH-16-0019/2016 H3N2-like virus, and a B/Phuket/3073/2013-like virus, which was from the B/Yamagata lineage.

They also recommended that the quadrivalent vaccines containing two influenza B viruses contain those three viruses, as well as a B/Brisbane/60/2008-like virus from the B/Victoria lineage. The VRBPAC met a few days later on October 4th, and the VRBPAC recommended for any US manufacturer that would make a Southern Hemisphere formulation to use the same formulation that the WHO had recommended the previous week. You can go to the next slide.

In the most recent Northern Hemisphere recommendation for the upcoming 2018-2019 Northern Hemisphere season was done earlier this past winter. The WHO recommendation was made on February 22nd, and that recommendation was that the following viruses be

used for trivalent influenza vaccines for the 2018-2019 influenza season for the Northern Hemisphere.

Again, an A/Michigan/45/2015 H1N1 pandemic 2009-like virus, an A/Singapore/INFIMH-16-0019/2016 H3N2-like virus, and a B/Colorado/06/2017-like virus from the B/Victoria lineage. The recommendation last February was that quadrivalent vaccines contain those strains, plus B/Phuket/3073/2013-like virus from the B/Yamagata lineage. VRBPAC met shortly after and on March 1st made the same recommendation as the WHO recommendation. Next slide.

Most recently last week, there was a WHO recommendation for Southern Hemisphere vaccines. This last week they recommended that egg based trivalent vaccines for use in the 2019 Southern Hemisphere influenza season contain the following. Again, an A/Michigan/45/2015 H1N1 pandemic-like virus, an A/Switzerland/8060/2017 H3N2-like virus, and a B/Colorado/06/2017-like B/Victoria virus.

They also recommended that egg-based quadrivalent vaccines containing two influenza B

viruses contain those three viruses and a B/Phuket/3073/2013-like virus from the B/Yamagata lineage. Next slide.

Today we will have a presentation by Dr. Katz and then the committee will discuss which influenza strains should be recommended for antigenic composition of the 2019 Southern hemisphere formulation of any influenza virus vaccine produced by a licensed US manufacturer. Next slide.

We try for the Southern Hemisphere for PAC and recommendations to make this a little simpler than for the Northern Hemisphere, and so what we'd like to do is just have two voting questions. One will be for a composition of a trivalent 2019 Southern Hemisphere formulation containing the three strains recommended by the WHO and do that as one voting question. And then a second voting question for the inclusion of a second B strain from the quadrivalent vaccines.

You can see the questions here. We'll bring them back up at the time the committee gets ready to discuss. I think that's it.

DR. MEISSNER: This is Cody Meissner. I wonder if I can ask a question.

DR. EDWARDS: Sure, go ahead.

DR. MEISSNER: Can you give us a brief history of how frequently the vaccine used in the Southern Hemisphere is different from the vaccine used in the Northern Hemisphere?

MS. HUNTER-THOMAS: I'm sorry, was that question posed to Dr. Weir or to Jackie Katz? Dr. Katz?

DR. MEISSNER: I think it was --

DR. EDWARDS: Dr. Weir probably.

DR. MEISSNER: Yes, I was addressing Dr. Weir because of his presentation, but whoever -- if anyone has some of that information I would be interested.

DR. WEIR: This is Jerry. I'll start. I don't know the exact frequency, but the influenza viruses are always changing, so it's quite common to see an update. In fact, if you looked at all of the strains that I put in for the last three WHO and VRBPACs, you'll see that there has been an update for

the H3 for the Southern Hemisphere now, compared to what the Northern Hemisphere used previously.

In the Northern Hemisphere recommendation last February, there was a change of the recommended B strain to be Colorado. I think previously the Southern Hemisphere, the Singapore strain was first recommended for the Southern Hemisphere before it was later incorporated to the Northern Hemisphere. So, it's sort of always changing.

I would say they differ well, almost -- fairly frequently there is a change in the Southern Hemisphere that would then be sometimes followed by a similar change in the Northern Hemisphere.

Jackie Katz might have more of an idea of how often it happens.

DR. KATZ: I would say I agree with Jerry that it's fairly frequent in the last number of years, primarily because a new variant is identified in either the Southern Hemisphere or Northern Hemisphere seasons and then is recommended as a vaccine component. And then the complimentary Southern or

Northern Hemisphere decision often takes up that same recommendation.

But as the viruses change, there is sort of a rolling cycle of the components changes. It's quite frequent I would say that they are not identical. And also, the recommendation for what is put in the trivalent can change and be different from Southern to Northern Hemisphere.

DR. EDWARDS: Thank you, Jackie. Are there any other questions?

Serina, does the hand raising work on the website so that if people want to ask a question they can punch the hand raising site, or does that not work?

MS. HUNTER-THOMAS: It does work, or if you just want to interject verbally. Either way is fine, we're flexible.

DR. EDWARDS: Great. Are there any other questions of Dr. Weir? If not, then I would like to introduce our next speaker, who actually needs no introduction as she is a real world leader in

influenza surveillance.

Jackie Katz is deputy director of the Influenza Division and the director of WHO Collaborating Center for Surveillance at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control. Jackie?

WORLD SURVEILLANCE PRESENTATION

DR. KATZ: Thank you, Kathy. I don't think I can point to any of the slides, is that right? I'll just ask for the slides to be forwarded.

MS. HUNTER-THOMAS: That's fine, Dr. Katz.

DR. KATZ: All right. Thanks. If we can move to slide 2 and the numbers are on the slides on the lower right-hand side. They are fairly small, but hopefully you can see them.

Just the background that was already introduced by Dr. Weir, this is work conducted by the Global Influenza Surveillance and Response System of WHO. This is a network of labs that are comprised by

six collaborating centers. One hundred forty-four national influenza centers, four essential regulatory laboratories, and multiple H5 reference labs, and we conduct year round surveillance for both seasonal and novel influenza viruses.

Last week in Atlanta was the first time we held a vaccine composition meeting in Atlanta at the CDC. We deliberated for three days and reviewed the data and came to our conclusions and recommendations that were then presented to industry on the 27th, last Thursday.

The group deliberating and making recommendations included the nine advisors. I chaired the meeting this time. And then we had 38 observers, many from different national influenza centers, obviously other collaborating centers, ERLs, and also our academic and veterinary partners, and other government partners. Next slide.

This is just an overview of all of the viruses and samples that have been processed by GISRS for the period we're talking about, which is February through

August or September, depending on when the viruses were collected. You can see here the red line indicates 2018 and you can see that early on in the season -- which reflects, of course, the Northern Hemisphere season -- the numbers of specimens processed by GISRS have reached an all-time high. This continues to be the case, particularly in the Northern Hemisphere.

As we taper off and move toward the Southern Hemisphere, just because of the nature of the fewer countries and fewer surveillance sites, these numbers diminish. If you'll turn to the next slide, slide 4?

This is looking now at WHO's data on the global circulation of influenza viruses. This is data that comes into their FluNet system that is reported by all of the countries involved in GISRS. On the right-hand side you can see the current year, the season through 2017-2018, the robust Northern Hemisphere season with the peak there around week four or five, and then it tapers off.

What I just want you to notice is towards the

right-hand side, we see quite a flattening. And comparing it to the left-hand side of the slide, the 2016-2017 season, you can see that the bump that occurred in weeks 21 through the end of week 35-36, it's much lower than the Northern Hemisphere but nonetheless, there was this robust bump. Most of it H3N2 viruses that we saw in last year's Southern Hemisphere season. By comparison and contrast, this year overall has been quite low activity. Next slide.

Among the viruses that were sent to WHO, this is the proportion by type and subtype. You can see in the orange there, roughly 50 percent of the viruses were influenza B viruses, and 50 percent were type A influenza. With the majority of those that had been subtyped, were (H1N1)pdm09 viruses. A much lower proportion of H3 and 2 viruses circulating, compared with what we saw last year. Next slide.

This just shows you similar pie charts, but now represented by the different regions and countries. You can see globally in the pale blue, if you just look over all of the pies, you can see that

there is quite a lot of pale blue. That's representing the (H1N1)pdm09 viruses, particularly in Central South America, parts of Africa, and Asia.

In contrast, the influenza B during this period, since February, was more predominant in North America, Western Europe, and some parts of Asia. Next slide.

This just shows the number of viruses that actually got sent to collaborating centers and were characterized by the genetic sequence analysis or by antigenic analysis. You can see the current period is shown in the green bars and that there is more H1 pdm09 viruses and the influenza virus is compared with H3 for this period. Next slide.

Now I'll be talking about the characterization of the (H1N1)pdm09 viruses. Next slide, please.

This shows you again the global distribution using WHO's activity breakdown where they break it down based on the epidemiologic activity reports by country. You can see the darkest red is widespread activity, and then the lighter the red or orange

color, the lower the level of activity. But you can see for (H1N1)pdm09 that there was quite a bit of widespread and regional activity throughout Mexico and South America and then in parts of West Asia and North and South Africa. Next slide, please.

This is now the number of (H1N1)pdm09 viruses that came into the GISRS network. You can see that they were lower than in the 2016 season, which was a big (H1N1)pdm09 season. Nevertheless, higher than other seasons in the Northern Hemisphere, and somewhat higher for the more recent weeks of the year. Next slide, please.

This is the number of viruses that actually were characterized by the different collaborating centers. You can see CDC in the US and the Crick in London, and VIDRL in Australia had more H1N1s in this period than in previous periods. Next slide, please.

This is a phylogenetic tree of the hemagglutinin gene. And this includes all sequence information available in the GISAID database for this period. The different viruses are color coded by the

region of the world that they are collected from. You can see that small map on the lower left tells you -- so the dark blue is North America, green is Europe, and then the other colors -- the sort of pinkish color -- is Oceania, orange is Africa, and so forth.

You can see I've tried to simplify this. If you look all the way down the bottom you'll see the Michigan/45/2015 virus in red, so that's the current vaccine component for both the past Southern and Northern Hemisphere vaccines. Essentially, all of the viruses that were collected during this period, with just one or two exceptions, still belong to the 6B.1 genetic subgroup.

Since about a year ago, these viruses have also included additional changes, which you'll see down at the very base of the tree. I'm sure you can't read it, but there are substitutions including a substitution at 164T. This is sort of a signature of the currently circulating viruses.

In addition, what we've seen in this past period is there is increasing genetic diversity of the

HA genes of viruses. Over 50 percent of viruses have acquired a change at Residue 183 from a serine to a proline, and this is being introduced multiple independent times. With each group, there are different additional amino acids that accompany that change.

In addition, at the top of the tree you'll see highlighted and boxed in, a change at 120. That's being seen quite a bit in Europe and now, increasingly in South America in their season. Again, the proportion of each of these different groups is rather small. There is one more additional subgroup all the way at the bottom with a signature of a change at 138 and 272. This group is really only seen in Asia, particularly in China and accounts for about one or two percent of the viruses circulating.

Although there is a change in the diversity that we're seeing, there is no clear winner. There is no clear genetic subgroup that is taking over. And so, we're carefully watching as these viruses continue to emerge and to determine whether one or other of

these subgroups that contain the 183P change or the 120 change, become a majority population. Next slide.

This is just another example. I put this in because it shows data from the Australian Collaborating Center. And you can see that many of the viruses from Australia, Southeast Asia, and New Zealand fall along the same lines. Again, they're all 6B.1 viruses. Many of them have this 183P change, which is about a third to half a way down that tree. But then there's multiple different changes and little subgroups, none of which are really taking the lead. No particular subcluster is winning the race at this point. Next slide please.

Now we're looking at the antigenic analysis of H1 viruses. This is hemagglutination inhibition assay data from the Melbourne Collaborating Center. Just to orient you again, what we do here is we identify reference viruses that represent the different genetic groups that we've been seeing and the ones I've talked about here. We raise ferret antisera to these reference viruses.

Along the top of this table are the different ferret antisera that have been raised against the viruses, which are the reference antigens along the first column there. We compare the ability of circulating viruses, or the test viruses, to react with these different ferret antisera. We compare their reactivity with the homologous titre of the reference virus, which was used to raise that antiserum.

Here we have virus from Australia, New Zealand, and a couple from the Philippines and -- I think that mostly covers it. If you look at the two columns that are highlighted in the darker yellow, the darker yellow is ferret antiserum raised to the egg-grown reference virus representing the vaccine composition virus, Michigan/45, and you can see there it has a homologous titre of 1280.

If you just cast your eye down the test viruses down that column, you can see that all of these viruses are recognized by this sera very well, within twofold of that homologous titre. And

similarly, if you look at the next column over, this is now ferret antisera to Michigan/45 that's been grown exclusively in cell culture. And we see the same thing, that the test viruses are all reacting with this serum similar to how the actual reference virus, the homologous cell-propagated Michigan/45 virus react to titres of 2560. If you look at the other antisera, essentially, the reactivity of the test viruses are the same as what I've just explained to you, indicating that we're not seeing any antigenic differences with the test viruses. Next slide please.

This is another hemagglutination inhibition table, this time from CDC's laboratories. I just wanted to highlight here, we're seeing exactly the same thing. If we look at our ferret antisera along the top there, either two egg- or cell-propagated Michigan/45. If you look three columns over, there's an antisera raised to New Jersey/13. That is a virus that contains that substitution at 183. But again, this antisera does not discriminate and does not show any antigenic differences with either the reference

viruses or the test viruses.

And finally, we also wanted to look with a pool of post-vaccination sera from adults that received the 2017-18 vaccine that contained the Michigan/45 component. If you'll look, that's highlighted on the right-hand side in the pale yellow. If you look at the titres against the Michigan/45 reference viruses there, either 640 or 320, and you can see that all the test viruses roughly have similar reactivity with that pooled post-vaccination human serum, suggesting that that serum is also not detecting any antigenic changes. Next slide.

This is just antigenic cartography. Again, this goes back to the HI data we produced that all of the collaborating centers produce using ferret reference antisera and you can --

MS. HUNTER-THOMAS: Dr. Katz.

DR. KATZ: Yes.

MS. HUNTER-THOMAS: The voice has dropped. Did you change position or anything?

DR. KATZ: Okay. I'm leaning. Maybe I

stopped leaning in. I'll lean in a little more. Is that better?

MS. HUNTER-THOMAS: Yes, much. Thank you.

DR. KATZ: Okay. The antigenic cartography slide. We're on slide 16, just demonstrates that viruses isolated from September 2017, to the current period August 2018, shown in yellow, are really in the antigenic cartography look exactly the same as the viruses in blue from the previous period. Again, this is in reference the big red dot represents the Michigan/45 cell-propagated virus. This is again telling us that using ferret reference antisera, we're not seeing any antigenic differences. Next slide please.

This is a summary of all of the antigenic data for the collaborating centers. This first table is comparing all of the circulating viruses tested, so over 1900 viruses, compared with the antiserum raised to the Michigan/45 virus propagated in eggs. You can see that we're seeing a vast majority -- 98 percent -- of these viruses reacting like the Michigan/45 egg-

propagated virus. Next slide please.

If we now do that same comparison but looking at Michigan/45 cell-propagated virus, we see again that we're getting 99 percent of over 2000 viruses tested that are antigenically like the cell-propagated Michigan/45 virus. Next slide.

As you know, the third component of what we do to characterize these virus is also take human serum panels from individuals that have received the most recent influenza vaccine component. In this slide -- this is data from one collaborating center from CDC. We looked at antisera from panels of individuals, adults or elderly; the adults are in yellow for Australian panels, green for a Southern Hemisphere panel from Peru, and blue is actually the Northern Hemisphere -- the last Northern Hemisphere 2017-18 serum panels. But we used pediatric population because it still contained the Michigan/45 component. We didn't have a pediatric panel for the Southern Hemisphere.

We used all of these panels and looked at a

number of different representative viruses that represent the different genetic groups we're seeing and circulating globally.

DR. LEVY: I have a quick question. It's Ofer Levy. Is it okay to ask a question?

DR. KATZ: Sure. Yeah.

DR. LEVY: Why is it that we don't have some of that pediatric data?

DR. KATZ: Because the WHO collaborating centers don't have a pediatric panel available. Australia historically has not done it; although, they're now looking into providing that panel and hopefully next year they will be able to. It's just an access issue and we're trying to rectify that, but getting these panels is challenging.

DR. LEVY: By getting the panel you mean having access to cohorts who can then be studied?

DR. KATZ: Correct. Yeah. And having the resources in-country and identifying a group that can conduct these studies and provide these panels. They need to be provided in a very timely manner because we

really need them to be vaccinated at the very earliest in the particular season.

MS. EDWARDS: Please make sure that you identify yourself before a question. The last questioner? Was that Ofer? No.

DR. LEVY: Yes, I did. I said this is Ofer. I'm sorry.

MS. EDWARDS: No, no, no, you did. But then was there another person that asked a question after that that didn't identify themselves? No, just please do so that we know who's speaking. Thank you. Go ahead, Jackie.

DR. KATZ: Okay. Thanks. If we look at this panel, we can see that if we look -- so this panel is comparing the response that was obtained to the reference Michigan/45 virus grown in cells. We do this because most of our test viruses are also grown in cell culture. You can see if you look at the pediatric panel, and then we also had an older pediatric panel. So, the pediatric was kids under 3 years of age. Older pediatric was 5-18 years of age.

And then the adults are 18-64 years of age, elderly 65 and older.

But you can see in general that compared with the response or the GMTs that we get to the cell-propagated Michigan/45/MDCK grown virus, we're not seeing any reductions below that 50 percent line. That 50 percent line is an arbitrary threshold that we use to identify reduced responses. If our geometric main titres for any given virus are below that threshold, they are considered significantly reduced compared to the vaccine reference virus.

Really the only reduction we were seeing, you could see at the far right-hand side, is the virus Switzerland/3330 and this is a virus that did have the 183 change and it had some additional changes. But unfortunately, because we have to do additional passaging for these in order to test against all of the panels, this particular virus had acquired yet another substitution that was not in the wild type virus and it was in a significant antigen excite. So, we can't really infer anything from that data.

Although it's reduced, it may well be because of that introduced mutation which isn't the actual wild-type virus. Next slide.

This is slide 20 now. This is now a compilation of all the data from all of the six testing laboratories that do the human serology analysis. This time we're comparing to the egg-propagated Michigan/45 reference virus. Here the color-coding has changed a little. Sorry about that. The adults are in blue. The older adults are in green -- and again these are Southern Hemisphere panels -- and the gray are children from the older Northern Hemisphere.

You can see that there are some reductions, but there is no consistent pattern with respect to a particular genetic subgroup being low. And, in fact, these reductions, where you can see the titres below the red dotted line, they're really just one off from one testing lab that weren't tested in other testing labs. If you look at the far right-hand side, where I boxed in all egg-grown and all cell-grown viruses, you

can see here that in both cases, the absolute average of all of the data is above that red line, suggesting that there is no overall significance in reduced titres when we compare these newer circulating viruses with the vaccine virus. Next slide.

In summary, for the H1 viruses, there was a predominance of H1pdm09 viruses in many countries, particularly in Europe, South America, parts of Africa and Asia. The vast majority of viruses had hemagglutinin genes that belonged to subclade 6B.1 and they had those additional amino acid changes at residue 74, 164, and 295. These are changes we've seen over the last year and have actually sort of swept through all of the H1 viruses circulating globally. Previously these weren't associated with any antigenic changes either.

So, in addition, we're now seeing greater genetic diversity in the hemagglutinin genes of H1 viruses with additional amino acid substitutions at 183, 120, and 138 but there's no clear predominant subgroup at the moment.

All of the recent H1N1 or almost all of the recent (H1N1)pdm09 viruses that were tested antigenically are similar to the egg- or cell-propagated Michigan/45 using post-infection ferret antisera in the HI test. When we looked at the human serology studies, again using HI, the geometry main titres of antibodies against the majority of recent representative viruses were not significantly reduced when we compared with either cell- or egg-propagated Michigan/45 virus. Okay. I wanted to move -- sorry.

MS. EDWARDS: Do we want to pause? Are there any H1N1 questions that people want to ask before you go on, Jackie?

DR. OFFIT: It's Paul Offit. Quick question, Jackie. The findings that you saw with the egg-based propagated vaccine wasn't surprising, right, regarding H1N1? Isn't it the H3N2 that primarily drifts during manufacturing eggs? Is that true?

DR. KATZ: Yeah, I wouldn't characterize it as a drift, but we have more problems with H3N2 egg-grown viruses acquiring additional mutations that can affect

their antigenic profile. Yes.

DR. OFFIT: Thank you.

DR. KATZ: Does that -- yep. Okay.

DR. MEISSNER: This is Cody --

MS. EDWARDS: It's nice to see these graphs. It's nice to see the egg and the cell culture data compared. Thank you. Go ahead, Cody.

DR. MEISSNER: Yes, and it's kind of a follow-up question to Paul's comment. Are those statistically significant different GMTs against egg virus and cell virus? Higher titre?

DR. KATZ: We typically see higher titres with the egg-grown viruses and that is in part because -- and we're just really starting to tease this out. We do believe that egg-propagated vaccines elicit a response not only to the relevant antigenic epitopes on the vaccine virus, that they may also in part elicit some responses to the epitopes that change due to egg adaptations. We typically see that egg-propagated viruses give higher titres because they were elicited by an egg-grown vaccine. Then we

typically see a difference with the cell-cultured derivative.

But the way we have to do this testing is we compare the cell-culture viruses so that's why we do a comparison both against a reference egg-propagated virus and a cell culture-propagated virus. We don't actually do detailed statistical analysis, but in some cases, I think these very low responses would be statistically significant.

DR. MEISSNER: Thank you.

MS. EDWARDS: Thank you. Any other questions? Okay, go ahead. Thank you, Jackie.

DR. KATZ: Okay, so let's move onto the next slide 23. This shows again the red line is 2018. These are the H3N2 viruses detected by the GISRS network. You can see that it's relatively low in numbers particularly for the period we're talking about. If we compare in the middle of the graph, the red line for weeks say 21-35, compared with the 2017 season in black, which was far more robust for H3N2. Next slide.

This shows, again, globally the level of outbreaks occurring according to WHO and, again, this is since February. This still does take into account part of the Northern Hemisphere season. You can see North America has quite an intense widespread and regional activity of H3N2 viruses. But for the Southern Hemisphere season is was far more regional. Countries in South America, Chile, and Paraguay had H3 predominating, but no other countries. Then you can see again some Northern Hemisphere countries in the darker colors, but for the Southern Hemisphere since February, not a lot of H3N2 activity. Next slide.

This is a phylogenetic tree again of the hemagglutinin gene. This is again old data that's available globally for this period. This is produced by our colleagues at the University of Cambridge. Just to keep this simple, we have identified again the number of genetic subgroups that are continuing to circulate.

For members who were there in February, you'll remember that this was becoming increasing complex in

terms of the number of different genetic subgroups that had emerged. It's become a little simpler just because some are predominating over others. Right now, if we look at the -- so most of these viruses are still within the 3C2A clade. There's a small group at the very top there that are referred to as 3A. These are the 3C3A group that continue to persist. If you'll remember back a few seasons, this was represented by the earlier Switzerland/2013 that was a vaccine component back in 15-16. These viruses continue to persist but at a low level globally, although we do see a number of them still in our past season in the US.

But what is predominating now is this subgroup within the 3C2a viruses. We refer to them as 2a2, and they have signature changes at residues 131, 142, and 261, which are identified there. And if you look again, the ladder just demonstrates by month what's circulating, and it's color-coded by region. You can see that for the period of February through July, we've got circulation a lot in the Northern Hemisphere

toward the end of our season, but also globally. The 2a2 viruses are predominating.

And the next genetic group, which is really also still in the mix, is the 2a1b viruses. These have diversified into a larger group that has a substitution at 135K and then a smaller but emerging group that have a 135N substitution. The other clade 2a4, 2a3, these are really not that highly represented, and this will be clear on the next slide.

We actually slice and dice the different propositions of these genetic subgroups by region globally. Just to highlight, the 2a2 viruses are in the bright pink, and you can see for Asia, Europe, North America, almost Oceania, and Central/South America, these viruses have predominated over this period. This is an increase in what we've seen compared with the Southern Hemisphere season and particularly Australia, New Zealand last season where they had different genetic groups circulating.

So, clearly, the 2a2 viruses are predominating globally now. The one exception is Africa, and you

can there's more of a mix of viruses. Typically, we see the older clades still in Africa. It seems like it's a bit behind the rest of the world in terms of the influenza viruses, and it's not quite at the leading edge.

The other group that I just wanted to call out is the group in red, the 2A1b, which have the 135K change and you can see that there in Europe, Asia, and Oceania, and Africa, they represent 20-30 percent of the viruses. Then, in the gold color, the 2A1bs, 135N, and although the numbers are extremely small for Oceania for the southern Hemisphere, there was a late increase in that group. But again, smaller proportions compared to the dominance of the 2a2 group globally. Next slide.

First of all, I'm going to give you the summaries of what we're seeing and for H3N2s. The performing hemagglutination inhibition assays is continued to be challenging because a lot of 2A group viruses don't have sufficient hemagglutination activity for us to test them in the HI. That's why we

now do -- are increasingly using virus neutralization assays as a supplement and to complement but also to test more viruses.

I'll first show you the HI data. This is again is a summary of four of the collaborating centers doing HI assays still. If you look at the right-hand side of this table, you can see that by Hi about 57 percent of the viruses tested were antigenically like the egg-propagated Singapore. You'll remember we changed from Hong Kong/4801 a year ago because Hong Kong/4801 egg-propagated virus representing the vaccine component at the time was no longer reacting well with circulating viruses.

You can see now that that number on the left-hand side of the table is as low as only 17 percent. So, the Singapore egg-propagated virus is still doing better, and that's why we chose it back a year ago. But it's not doing as well as we would like. Next slide.

This now is looking at the same analysis but now comparing in an Hi assay still how similar the

circulating viruses are antigenically to the cell-propagated Singapore virus. Here you can still see that 95 percent of these viruses are antigenically similar to Singapore cell-propagated. So, the problem we're having is again with the egg-propagated viruses. Next slide.

This should be slide 29. This now is virus neutralization data again comparing to cell-propagated virus. You can see, if you look on the right-hand side, you can see that 91 percent of viruses tested by all of the centers still showed antigenic similarity to Singapore cell-propagated virus. Next slide.

And then, finally, this is virus neutralization data now comparing the circulating viruses against the egg-propagated Singapore. You can see it's reduced. It's not as bad as it is by HI. Overall, 72 percent of viruses still showed similarity with the egg-propagated Singapore virus, but there's some great diversity in the results that were obtained by different collaborating centers. This reflects, if you'll see that asterisk that I put there, what we

found is that the egg-propagated Singapore viruses that were being used in different collaborating centers had heterogeneity at a particular substitution that was driven by adaptation to eggs.

We know for the candidate vaccine virus -- so if the virus is propagated in eggs, made into a reassortment, and then used as the vaccine virus, we know that that vaccine virus contains a predominance of 225G. So that is what we think is truly representative of the egg-propagated vaccine.

We believe that the higher reactivities then that we see for say CDC, CNIC, NIID, Japan, and VIDRL in Australia reflect the fact that we've heterogeneity at that site. We can't be sure that we're really, totally representing the egg-propagated vaccine properly.

At the London lab, shown highlighted in the yellow, they were able to clone a virus that only had 225G. We also tried that CDC. We just could not get a purely prodinal virus at that substitution. And so, when they do that, they see that they see very

different patterns and that all of the viruses that they tested are actually not reacting well with the egg-propagated Singapore virus. Next slide.

And so, this is actual data now reflecting that. This is a neutralization assay from the London Crick Laboratory. You can see highlighted in yellow is the antisera raised to the Singapore egg-propagated virus with high homologous titre of 2560 in red. If you cast you eye down to the test viruses, you can see that the titres are all very low compared with this homologous titre.

In contrast, the next column over, not highlighted, is antisera raised to cell-propagated Singapore. You can see that the homologous titre of the test viruses are much better, much higher and more comparable to the 1280 homologous titre.

I want to draw your attention to the far-right column. This is highlighted in the pale yellow. It's antisera raised to a contemporary 2a2 virus Switzerland/8060 and this is an egg-propagated virus. You can see here that if you look at the lower part of

the test viruses and these are all 2a2 viruses, you can see that this antisera to this new egg-propagated virus covers the circulating 2a2 virus very well. However, above that you'll see the less than sign. These are titres against 2a1b viruses and that this particular antisera doesn't cover that minor subgroup very well. Next slide.

This is additional data. This is CDC virus neutralization data. Just to show you a similar picture with the cell-propagated Switzerland -- that's the one in dark yellow -- you can see the antisera to cell-propagated Switzerland has a homologous titre of 2560, and the vast majority of viruses are well inhibited by this antisera. Again, saying that antigenically, the Singapore viruses cover circulating viruses quite well. This is also demonstrated in the next column. QMC stands for Qualified Manufacturer's Cell.

This is the MDC case cell line which is used to isolate viruses for the cell-based vaccine production. This North Carolina/4 is actually the

cell-based vaccine component for the Northern Hemisphere cell-based vaccine. You can see again -- so it's a Switzerland-like virus in the 2A1 genetic group. You can see again that this antisera covers the circulating viruses quite well, including viruses in different genetic groups.

In comparison, an antisera raised to a more contemporary 2a2 virus in the far right-hand side, again, like what I showed you in the previous neutralization table, it covers other 2a2 viruses very well, but it doesn't cover the minor genetic groups like the 2a1b group.

So, that was important for the decision to be made about the cell-based vaccines. I know that's probably not something you're going to have to consider based on the questions that Dr. Weir posed to you. Moving to the next slide. Slide 33.

This is looking at this by antigenic cartography. Maybe this is an easier way to look at this. This is hemagglutination inhibition data in this figure. Again, the pink bubble there that you

see reflects the different relative antigenic position of Singapore egg-propagated viruses that we saw in different collaborating centers, so a bigger overall area meaning that in some labs the antigenic distance was smaller and in other labs it was larger. But you can see here that shown in yellow, these are the 3C2a2 virus that are predominating globally. These are closely around the Switzerland/8060 reference egg-propagated virus and are a little more distant from the Singapore cell-propagated virus in the dark red. You can see that there is antigenic distance and difference between them.

DR. LEVY: This is Ofer Levy. Is it okay to ask a question?

DR. KATZ: Yeah, sure.

DR. LEVY: Looking at the antigenic cartography image, in terms of the X and Y axis, is this just a way to separate out the data? Is this like a principal component analysis? Or what kind of plot is this exactly?

DR. KATZ: Each square represents the two-

fold. It's really just taking the hemagglutination inhibition titres and doing sort of a cartographic analysis using a particular software, which I can't think of the top of my head, but essentially it's a more complex analysis. It takes every virus and serum interaction into account to get this sort of like a two-dimensional picture.

DR. LEVY: And when you say that there were differences between the different labs and the distances detected -- that went by a little quickly. Were you implying that there were differences in the way the labs were running assay or you're just implying that they're working with different viruses and, therefore, those viruses displayed different distances?

DR. KATZ: Right. So that's going back to the what I described for the egg-propagated Singapore viruses. Although each lab tried to have a pure clonal virus, it's just very hard to do to get all the viruses that are exactly the same. We know that there's substitution. This egg adaptive change at

residue 225 does play a role in antigenic profile. We know for sure that the data from the London lab was based on a virus that was totally clonal at that position. Whereas, other labs, it was more like a mixture. We know that the viruses were mixed up.

DR. LEVY: It's not technically feasible for the labs to share with one another, the isolates to test one another isolates?

DR. KATZ: No, because as soon as you grow it up, it's going to change again. So, each lab has to grow up sufficient quantity to be able to test over a whole season. You can clone it out and then still grown it up, and you'll still get a mixture. That's what happened in our case. So, it's not really -- I mean that might be something that we have to look into in the future, but the way it's done --

DR. LEVY: No, just thinking if London is able to grow a single pure preparation, is there any way to stabilize that or preserve it and share some of it so that the different labs can send it?

DR. KATZ: It would be very difficult for them

to grow sufficient quantities for all labs and they could share their virus, but as I said, as soon as another lab grows it up, it could change. And this is just a particular challenge we recognize this time. It highlights the importance of knowing exactly what virus is put into a ferret and what the sequences of the virus that goes into a ferret for the antisera and what is used for the antigen. Because for H3N2s, subtle changes can make a difference. Okay, so next slide.

We should be on -- so this is the neutralization assay. This is just really using now the neutralization titres for all of the laboratories and this list data because we don't test as many viruses. But you can essentially see the same picture and the distinction between the 2a2 and 2a1 and all the 2a viruses as well as the 3C3A viruses, which we know are clearly antigenically distinct now. Next slide.

This is slide 35. This again using now the panels of human sera from adults and older adults that

were vaccinated in Australia and Peru. This is a summary or a compilation of all of the labs' data, all of the labs that were testing, a compilation of the results compared with using cell-propagated Singapore virus as the reference. So, that is set so its GMT is set at 100 percent and we look at the relative GMT for the other viruses. You can see many of the cell-propagated viruses are lower, particularly in number of the 3C.2a2 and 3C.2a1b viruses. If you look at all 2a2 viruses there at the far right-hand side, you can see particularly for older adults that it's sort of is just on the borderline of a 50 percent reduction overall. Whereas, the 2A1b viruses faired a little better. Next slide.

In summary of H3N2 viruses are continuing to evolve, two subclades are predominant now. The 2A2 is predominating globally in recent months, but there's also to 2a1b group. They represent a far smaller proportion of viruses circulating globally. So, the 2a2 viruses are antigenically distinguishable from former 3c2a subclades and from viruses within the 2a1b

group because antisera to the 2a2 viruses does not cover well this smaller genetic 2a1b group.

Antisera raised against egg-propagated Singapore -- when it was similar to the vaccine virus -- so this speaks to having the same substitution that we know is in the candidate vaccine virus used in the vaccines. Then we see that the circulating viruses are not well recognized by this antisera. But antisera against the 2a2 viruses themselves recognize other viruses in that subgroup very well, but do not recognize the other minor subclades well.

However, we do see that for the cell-propagated 2a1 virus, which is being produced in qualified manufacturing cells and which represents the reference virus or the cell-based vaccine component of the Northern Hemisphere cell-based vaccines, these do recognize a majority of circulating viruses. In the human serology neutralization tests, we saw that the geometric main titres against several of the recently circulating 2a2 and 2a1b viruses were significantly reduced when we compared them to the GMTs we got with

the cell-propagated Singapore vaccine reference virus. So, are there any questions for H3N2? I'm sure there are.

MS. EDWARDS: Yes, it's somewhat problematic isn't it?

DR. KATZ: It is. Well, we could come back to it. I could let you digest it a bit, and I can go on to the Bs.

DR. MONTO: This is Arnold. I'd like to ask a question.

DR. KATZ: Mm-hmm.

DR. MONTO: How many of the viruses that were circulating here in the US were 3C2a2?

DR. KATZ: I think it was well over 80 percent.

DR. MONTO: So, in fact, we did have somewhat of a mismatch beside the egg adaptation issue?

DR. KATZ: Possibly, but that was compared with the older -- remember we had Hong Kong/4801 in our vaccines still.

DR. MONTO: In our vaccines? Oh, so we didn't

have the Singapore in the vaccine. But going forward we will --

DR. KATZ: No, that's in the vaccine that for this.

DR. MONTO: So, going forward, if we do get H3N2, we are going to have a bit of a mismatch in addition to --

DR. KATZ: It's possible. Yes.

DR. MONTO: Hopefully, we're going to have H1N1.

DR. KATZ: Right.

DR. MONTO: No comment necessary.

DR. KATZ: Okay.

MS. EDWARDS: This is Kathy. Is that what happened in the UK with the H3N2 this year?

DR. KATZ: They had, again, predominantly 2a2. They did have an additional substitution that was not seen widely elsewhere. I think it was seen a little bit in Europe and the UK. It's the same substitution that did affect the antigenicity, but I can't speak to the VE for H3N2 is always low. To what degree is

antigenic change because the virus has changed or the antigenic change because of the egg adaptation, it's hard to tease out.

MS. EDWARDS: Thank you.

DR. KATZ: Any other questions?

MS. EDWARDS: Why don't you go on to the Bs then, Jackie.

DR. KATZ: Okay. Moving on to slide 38. Here again you see the global picture and again there was a lot of B activity in the Northern Hemisphere season particularly late in the US had predominately B after March, so that's reflected by the widespread outbreak dark red color. But also, there were pockets of B activity regional and local activity in Southern Hemisphere and tropical areas over that period since February. Next slide.

Again, the Northern Hemisphere B season was very robust as shown by the red line and then has again tapered off in the Southern Hemisphere season. Next slide.

Again, this is the number of influenza B

viruses overall characterized in the different collaborating centers from February to August. Again, more in London and generally lower than in previous seasons but still a lot of influenza B. Next slide.

And this is the breakdown for where lineage is determined. The B/Yamagata viruses were still predominate at about 78 percent and B/Victoria lineage viruses were only 22 percent of all of the B viruses when we have the lineage determined. Next slide.

And let me talk about the B/Victoria lineage viruses first. Next slide.

Again, this is a phylogenetic tree of the hemagglutinin. It's a large tree that encompasses all of the genetic data available. As similar as before, if you focus on the sort of bottom right-hand side, you can see the columns here represent the viruses circulating by month color-coded by the regions. You can see that there's quite a bit among the B/Victoria. Most of the viruses are falling into this lower part of the tree. That represents the viruses that have acquired a two amino acid deletion in the

hemagglutinin. These are the viruses we talked about last time in early March for the Northern Hemisphere decision. These are what we refer to as the 1A.1 viruses.

The rest of the viruses still fall into the clade 1A, which is represented by Brisbane/60 which has been a vaccine strain. You can see interjected along here is three little purple bars representing viruses that have triple deletions so three amino acid deletions in that same region of 162-164 an antigenically relevant site. You can see that they're on different parts of the tree, and this tells us that they are separate introductions. They're occurring independently in different viruses in different parts of the world. Next slide.

Again, this is a pie chart, so we understand the proportions of viruses within the B/Victoria lineage only now that are this double deletion or the V1A.1 group shown here in the yellow color. You can see in Europe, North America, and Central/South America these viruses are now predominant. In

Central/South America, during their Southern Hemisphere season in South America, these are the only B/Vic viruses we isolated. We have seen a few viruses in Oceania; although, it's slow to emerge there and it's now emerging in both Asia and Africa.

Shown in the dark red are the viruses with the three amino acid deletions, and these are seen very sporadically. We have a couple from Africa. The overall numbers of viruses there are extremely low. We did have some from Asia but not in this reporting period. And then we did see our first triple deletion in North America at the tail end of our season, and this was from a traveler from Africa. We believe this is an introduction from the African triple deletion viruses. But the bottom line is the double deletion virus has slowly increased and, according to our predictive modelers who attended the meeting, is expected to take over the B/Victoria lineage overall. Next slide.

This is just another to break down to tell you exactly which countries these viruses are emerging in.

But essentially, we've seen over 380 double deletion viruses now in 43 countries. Next slide.

Now this is an antigenic analysis now using the hemagglutination inhibition test. This is data from the collaborating center in Melbourne. If we look at the far left-hand side, you can see antisera raised to the Brisbane/60 self-propagated virus. This is representing the Brisbane component, which has been the B/Victoria lineage component of vaccines for quite a number of years.

You can see there, if you cast your eye down, the test antigens, you'll see a few viruses that have V1A next to them. Those viruses in general are still well-covered by the Brisbane/60 antisera. But, if you look down further, you'll see titres of less than 20. These are mostly with viruses that are the either the double deletions the V1A.1 or they're some pair of viruses there from Cambodia. The V1A.2, they have the triple deletion.

If you now look towards the right-hand side, I've tried to put in a green box. I don't know how

well it came out, but the antisera raised to these V1A.1 viruses so the viruses that have the double deletions. You can see if you look down, this antisera doesn't react well with the older V1A, the Brisbane-like viruses. But it does cover the double deletion viruses quite well.

However, in general, it does not react well with the triple deletion viruses, so these are antigenically distinct again. This is shown also in the next column, which is highlighted in the blue box. This is antisera raised now to a virus that has the triple deletion, a virus from Hong Kong. You can see that it only reacts well with the Cambodia viruses, which are very similar and have that triple deletion. But it doesn't react very well with any of the other circulating viruses, so we have a number of different antigenic groups.

If you turn to the next slide 47, you can see this is broken down in the antigenic cartography where the old viruses that are still within clade V1A and Brisbane/60-like are shown in the gold. That's the

most recent viruses circulating up to August of this year and then the older viruses in blue. They are squarely focused around the Brisbane cell-propagated virus.

But if you look down to the viruses in dark orange, these are representing the Colorado/06-like viruses and Colorado/06 is the reference virus representing these double deletion viruses. You can see they form their own cluster. Then in purple, just the sporadic purple dots representing the triple deletion viruses, and they are distinct from both the Colorado-like viruses and the Brisbane-like viruses. Next slide.

This is the summary of the HI reactivity from all of the collaborating centers. Again, testing over a small proportion of viruses because B/Victoria didn't circulate that heavily. If you look on the left-side and this is comparing to egg-propagated Brisbane/60, you can see only 37 percent of the viruses are reacting well with that antisera. The majority, 63 percent of viruses, react poorly at

titres that are eight-fold or greater reduced. The reciprocal is really true now if we look at the reactivity compared with the Colorado/06 reference virus representing the double deletion variance.

You can see the majority now 68 percent of viruses, roughly two-thirds of viruses, are well covered and only one-third of viruses are poorly inhibited. That one-third represents still either the very low number of triple deletion but mostly it represents the older B/Brisbane-like viruses that are still circulating. Next slide.

This is a serology study now. Looking at the panels I've previously described to you, this is again a compilation of all of the viruses tested by all of the centers and where it's doing the testing. This is comparing the response for the geometric mean titre against the egg-propagated B/Brisbane/60 which was in the vaccine for all of these panels. You can see that a number of double deletions and triple deletion viruses are giving quite poor responses. When you look at all of the double deletion viruses,

particularly the panels from children are quite reduced, and the panels from the adults are sort of borderline. All of the triple deletion viruses, they're giving very poor GMTs relative to the egg-propagated B/Brisbane.

Similarly, if you compare now against the cell-propagated virus, you see generally the same pattern. There's still some reduction. It's a little less pronounced because comparing the test viruses, which are generally cell-propagated now comparing it to the cell-propagated Brisbane, the difference is not quite so extreme. We're still seeing a reduction particularly in the panels from children that received B/Brisbane. Next, I'll move on to the Yamagata. Next slide and the next slide again.

The B/Yamagata, this is again is a phylogenetic tree of all of the hemagglutinin genes. If you just cast you eye back to what the H3s were doing with all of this branching, the Yamagata phylogenetic tree is still fairly linear and homogenous. There's really very little evidence of

genetic diversity and no significant genetic subgroups emerging. All of these viruses, although there was a very robust B/Yamagata season globally, they all are fairly genetically similar and belong to the Y3 clade. Next slide.

This is now showing the antigenic characterization using the hemagglutinin inhibition assay from the CDC lab. Highlighted in yellow at the left-hand side, you can see antisera raised to the reference Phuket/3073 virus, which is representing the vaccine, the Yamagata vaccine component. If you look at antisera raised to cell-propagated MDCK cell-propagated, you see that all of the test viruses here from the US, the Middle East, Africa, Asia, and Central America, they're all well-inhibited by this antisera.

If we look to the left of that antisera raised to egg-propagated Phuket, we see in general that these viruses are still well covered. More viruses are showing a four-fold difference, but they are not showing a greater than eight-fold difference or

greater than or equal to eight-fold difference, which is our criteria for saying something is antigenically different. Next slide.

This is just now showing this using antigenic cartography to visualize this. This is all the data from all the collaborating centers. You can see that the Yamagata viruses from the last year from September 2017 to August 2018, represented by the yellow dots, that they're really not moving antigenically. They're still close to the Phuket cell-propagated virus and they're right on top of the older viruses shown in blue from the previous year from 2016-17. Next slide.

This is a summary of all of the data from the different collaborating centers. On the left-hand side, we're comparing against the egg-propagated Phuket/3073 reference virus at 90 percent of viruses are antigenically similar to this. If we look on the right-hand side, we can see that 99 percent of viruses are antigenically similar to the cell-propagated Phuket. So again, no evidence of antigenic drift from the Yamagata viruses. Next slide.

This is the human serology data again for all of the testing laboratories. All of the data is compiled together for the different panels of adults, older adults, or children that would have received a recent vaccine containing the B/Phuket/3073 component. Again, this is comparing to the cell-propagated virus shown by the red arrow. You can see with a few exceptions -- and this Guyane virus is an exception, it's an egg-propagated virus that had acquired some changes. Most of the other virus are showing that the panels of sera are giving GMTs that are less than 50 percent different from the reference cell-propagated B/Phuket and that includes the panels of children's sera. Next slide.

In summary, for the B viruses overall, both the Yamagata and B/Victoria lineage have cocirculated, but the B/Yamagata lineage has predominated globally. Next slide.

For the B/Victoria lineage viruses, all of these viruses belong still to genetic clade 1A. A steadily increasing proportion of viruses from many

countries now have this double deletion at amino acids 162 and 163 in the hemagglutinin. There's a smaller group of viruses from only a handful of countries at this point that have a triple deletion at this site 162-164 in the hemagglutinin.

So recent viruses that don't have any amino acid deletions, were still well inhibited by ferret antisera raised to B/Brisbane/60 viruses. Viruses that do have deletions, either two amino acid or three amino acid deletions, are poorly inhibited by ferret antisera raised to the cell cultured B/Brisbane/60 virus. Most viruses with a deletion of the two amino acids in the HA -- this is the V1A.1 genetic subgroup -- react well with ferret sera raised against the B/Colorado/06 reference virus. But the exception is that the delete viruses with three deletions, the triple deletions, they are not well-inhibited by this antisera.

So, with human serology studies, which we performed by HI analysis, the geometric main titres against the tested B/Victoria lineage viruses,

including those with two or three amino acid deletions and the HA, were modestly reduced compared to the HI titres to either the egg or cell-propagated B/Brisbane/60-like viruses.

For the B/Yamagata lineage viruses, all the HA genes belong to the genetic clade 3 and we're seeing very little genetic diversity within this clade. Recently circulating viruses were well inhibited by ferret antisera raised against either the cell culture- or the egg-propagated B/Phuket/3073 viruses. In human serology studies using HI, the geometric main titres against most of the representative viruses were not reduced compared to the HI titres to the cell-propagated B/Phuket reference virus.

I can stop there and answer questions before I just go on to remind you of the recommendations again. Or I can just finish off and then take questions.

MS. EDWARDS: Are there any B questions, to be or not to be. Why don't you go ahead, Jackie, with the rest.

DR. KATZ: Sure. Just really one more slide

reiterating the recommendations that Jerry mentioned earlier. For the egg-based Quadrivalent influenza vaccines, the recommendation was to include a Michigan/45/2015(H1N1)pdm09-like virus; A/Switzerland/8060/2017(H3N2)-like virus; a B/Colorado/06/2017-like virus, which is just a B/Victoria/2/87 lineage; and the B/Phuket/3073/2013-like virus, the B/Yamagata. For egg-based Trivalent vaccines the Michigan/H1N1 and the new Switzerland/H3N2 component were recommended and the B/Victoria lineage B/Colorado/06/2017-like virus was recommended for inclusion.

Just to let you know this probably does not affect your decision, but the decision was made for non-egg-based vaccine viruses that there should be no change for the H3N2 component. That is should remain the Singapore/INFIMH-16-0019/2016-like virus. And I've got a typo there. The other components would be like the egg-based vaccine.

MS. EDWARDS: Thank you, Jackie.

DR. KATZ: That's it.

MS. EDWARDS: This is Kathy, Jackie. Is this the first time that you've had to make a different recommendation for the egg-based and cell-cultured based vaccine for the WHO?

DR. KATZ: Yes, it is and that's why I focused on the CDC neutralization data because we really -- if you compared to either the cell-propagated Singapore reference virus or the actual candidate vaccine virus that's used in the cell-based vaccine, they still cover the circulating viruses fine. So, we really didn't have a justification to move away from the Singapore recommendation for cell-based vaccines.

MS. EDWARDS: Thank you. Other questions?

DR. KURILLA: This is Mike Kurilla. I just want to make sure I understand this. The voting questions were of value were asked about the non-egg-based composition is not on the table?

MS. EDWARDS: That's correct.

DR. KATZ: Yeah, Jerry, do you want to comment?

DR. WEIR: That's correct. We were trying to make it simple because the recommendation really only

applies to one manufacturer who makes an egg-based vaccine at this time.

DR. KATZ: Others' questions?

MS. EDWARDS: Well, if there are no other questions, then certainly Jackie would entertain any. This is the time that we were to take a break. I think that given the fact that the voting and this additional discussion will be forthcoming. I think we probably do need a break, but I'm not sure that it needs to be a lunch break, maybe just a bathroom break. Would that be fine with everyone, or do people want a lunch break for the 45 minutes that's on the schedule?

UNIDENTIFIED MALE: Well, for those of us who are on the West Coast now, it's not lunch.

MS. EDWARDS: Exactly. It's just a breakfast, right?

UNIDENTIFIED MALE: You're right. A late breakfast.

MS. EDWARDS: Would it be fine for us to have a shorter more truncated bathroom break than a lunch

break?

UNIDENTIFIED MALE: Sure. It's fine with me on the East Coast. That's fine.

MS. EDWARDS: Okay. All right.

UNIDENTIFIED MALE: That's fine with me as well.

MS. EDWARDS: Perfect. So, let's do that. Let's meet then in -- is 15 minutes fine? So, then that will be five minutes after the hour.

UNIDENTIFIED MALE: Sounds good.

MS. EDWARDS: Okay. Thank you and we'll regroup then.

UNIDENTIFIED MALE: Perfect. Thank you.

[BREAK}

NO OPEN PUBLIC COMMENTS REGISTERED

COMMITTEE DISCUSSION

DR. EDWARDS: Let’s get started. There are no registered public speakers, so we will forego the open public hearing and move directly to the committee discussion. We will need to be voting on these two

questions, which are think are now in front of us or will soon be in front of us. Then we can begin to discuss and comment about them. And we can ask questions or make comments and then we can actually go around, and people can offer their comments. Are there any general comments that individuals have?

DR. TOUBMAN: Bear in mind I'm the person who doesn't understand most of this stuff, so I'm just trying to figure it out. In terms of the specific recommendations of quadrivalent versus trivalent, this is where perhaps it's ideal, the quadrivalent vaccines, but where for whatever reasons it's only going to be trivalent, then you make the choices, right, of what is the best? In this case, you pick only one B virus vaccine, as 2S would be in the quadrivalent. If I have that right.

My question is this. The summary says that Yamagata prevails substantially over Victoria, I guess, worldwide. And if that's the case, why when you make the case for the trivalent, where you have to choose one of the two B vaccines, why do you choose

Victoria instead of Yamagata if Yamagata is more prevalent?

DR. KATZ: I can address that, and it's a really good question. It's something that the committee that makes the WHO recommendations really struggle with. The rationale is the same as the rationale that we used in February; and even more so now because we've had the continuing circulation of the Yamagata.

We believe that true, either infection, or in some cases vaccination, there's probably quite a bit of population immunity now to the B/Yamagata lineage viruses. In contrast, the B/Victoria and particularly because there's a new drifted variant that is now emerging globally, we believe it's important to put it in the trivalent vaccine for individuals, particularly, young children who might not be exposed to any B viruses previously, so they would really need some immunity. And we felt it was best to put in the emerging virus so that they have the best possibility of gaining immunity to this new virus that is emerging

globally.

That was the rationale back in February and it's still the rationale for the Southern Hemisphere decision. Of course, this is a national decision and different countries can change that. But we really cannot predict what is going to be predominating next year. We know that the V/Victoria tend to predominate every third or fourth season, but there's no really good way to predict this. We just felt that the B/Yamagata have been circulating and predominating now for quite a while, and it was reasonable to put the B/Victoria lineage virus in the trivalent vaccine.

DR. EDWARDS: Thank you, very much. That was an excellent question Sheldon.

DR. TOUBMAN: I actually have a follow up, though, if I may. The follow up question is, it sounds like you said there was quite a bit of discussion about this. Is there a count prevailing view or was this pretty much consensus; that for the reasons you said, that it made more sense to go with B/Victoria in the trivalent?

DR. KATZ: There was discussion. The predominant view was the one on which we made the recommendation.

DR. TOUBMAN: It was the predominant one, but there were people who thought otherwise?

DR. KATZ: I can't make that public, but I can just tell you it was the predominant opinion.

DR. TOUBMAN: May I ask, for those who did not share that view, what their concerns or argument was?

DR. KATZ: It was similar to your concerns about the predominance of B/Yamagata; which is the current and past predominance. And as I said, we cannot predict what's going to happen next year or even this season, for the Northern Hemisphere.

DR. TOUBMAN: In the discussions, I assume that the people who raised the concern that I raised, that the Yamagata is more prevalent right now, the discussions on the other side were, yes, but that's been around for a while so there is some protection on that; whereas, we don't have that for Victoria. I assume that was in the discussion. And I'm just

trying to figure out when that was discussed, whether minds were changed. And that's true in that there's a real reason to make sure we get this Victoria out for the reasons you outlined?

DR. KATZ: Ultimately, that was part of our discussion and it was what the final recommendation was based on.

DR. LEVY: Is it okay if I ask a follow up question on that topic?

DR. EDWARDS: Yes, please.

DR. LEVY: One question is in arriving to these decisions, which are obviously complicated, does WHO ever make use of computer modeling or artificial intelligence approach to model this?

DR. KATZ: We are currently working very closely with two different modeling groups that use all of the genetic data that I've explained to you is available to them. And the collaborating centers are also now sharing their antigenic data. And so, they are doing their own fitness forecasting. And their predictions are really taken into consideration for

the final recommendations. And for the first time, they were invited to attend in person and present their data, in person, last week in Atlanta.

DR. LEVY: And did their data support the third-stain selection that we're discussing now?

DR. KATZ: In terms of the predominance of one over the other -- other B lineage? Is that what you're asking?

DR. LEVY: No. Did their presentation support the decision in the trivalent to include the Victoria lineage?

DR. KATZ: They again cannot predict -- and they were asked this question. They cannot predict which lineage is going to predominate. They do predict that the B/Victoria variant, represented by the B/Colorado/06/2017 virus, is going to become the dominant B/Victoria lineage virus.

DR. LEVY: So, basically that is an effort to stay ahead of the curve, essentially?

DR. KATZ: Yes. Yes.

DR. EDWARDS: I wanted to ask a question in

terms of what is the breakdown of the vaccine trivalent versus quadrivalent in the Southern Hemisphere? I mean, certainly the Northern Hemisphere.

DR. KATZ: That's a really good question and we don't have that data. And we realize that that was something that we needed to tabulate better. We believe that a lot of South America is still using trivalent. We did have a representative from Costa Rica and he informed us that they were moving to quadrivalent. We know Australia and New Zealand have moved to quadrivalent. But there are parts of Africa, and other regions in the Southern Hemisphere, that we felt that predominately they still might have teeth at trivalent.

DR. MONTO: Since this refers to US sold vaccine, how much trivalent versus quadrivalent vaccine is actually produced by the manufacture, in the US, that we are regulated?

DR. KATZ: That would be a question for Jerry, I think, for the particular manufacture related to

this decision. Overall, for the US over 75 percent of the vaccines that were used last season is quadrivalent, and that's increasing every year.

DR. WEIR: It's kind of a complex answer. The manufacturing in question is licensed to make either a trivalent or a quadrivalent. What they make and distribute in the use for the Northern Hemisphere, I think, is almost all quadrivalent now. They're not here so we cannot ask them.

But the reason it's difficult to answer is because I don't know what their plans are to what they will make and try to distribute as part of this Southern Hemisphere recommendations. And it could actually be different from what they do in the US for the Northern Hemisphere. So, anyway, they're licensed to make both. I don't know what their plans are for the Southern Hemisphere.

DR. EDWARDS: Are there any other general questions before we actually go around to each individual person and they can make their comments and statements. Any other general questions?

DR. KURILLA: One question for Jackie. Is there any population immune surveillance data that would support the degree of immunity to the Yamagata over Victoria?

DR. KATZ: That's a great question. That's something, again, that we're moving towards having more comprehensive population immunity data, but we're not there yet. Definitely, it was not available for us to review, but we are aware that a few countries do look and do these types of studies. But we didn't have that data to analyze. So, it would have been very localized, not very regional or global representation.

DR. KURILLA: I think your reasoning sounds very straightforward and reasonable. But you're making the assumption, that the population level immunity to Yamagata is based on the prevalence of past exposure that you presumed happened.

DR. KATZ: Right. Yeah, you're right. And having some real seroprevalence data would be beneficial.

DR. EDWARDS: Are there any other questions?

DR. JANES: Jackie, I'm sure it's in your presentation somewhere, but can you comment on the cross reactivity of the Yamagata and Victoria lineage and how that pertains to this choice?

DR. KATZ: In young children we don't see that much cross reactivity, there's sort of lineage specificity. With increasing age, as individuals are actually infected with one or the other, you do see more cross reactivity. I'm just thinking -- I don't know that we can tease it out of the serology that we had, because I think it got taken out. We didn't include, for example, a trivalent if it didn't include -- in the Southern Hemisphere -- if it didn't include B/Victoria.

But there was some cross reactivity, you do see boosting. It would have been the case where the trivalent vaccine that included B/Yamagata for the last Southern Hemisphere season did boost responses to B/Victoria. We didn't have the reciprocal -- well, there was also cross boosting with -- I don't know if

we had the example of a trivalent only. Oh, yeah, we did; we did in the older adults in the US because they were only TIV.

So, yeah, you do see it both ways, but you don't see it again for young children. Because the cross boosting is probably based on the sort of preexisting immunity and infection with one or other or both lineages.

DR. JANES: Thank you.

DR. KURILLA: Jackie, one more question. Is there any recognized difference in virulence or severity of infection by Victoria versus Yamagata?

DR. KATZ: We couldn't say that the new double deletion B/Victoria had -- the data was just very limited, and we couldn't say that it was causing more disease. We do know it's a B/Yamagata this season, generally, that it did hit older adults and we were seeing hospitalizations due to B/Yamagata. But again, it's because B/Yamagata was circulating. So, the relative difference between the two, I don't think we have data on that.

DR. GREENBERG: Can I ask a question about the H3N2 summary?

DR. KATZ: Sure.

DR. GREENBERG: I want to make sure that I understand the relatedness between the strains, the viruses and what we're talking about in terms of changing from the Singapore to the Switzerland. The Singapore is representative of which clade; is that the 2a2?

DR. KATZ: No. Well, Singapore is, if you think about the phylogenetic tree, it's sort of lowered down. It is a 2a1 -- 3C.2a1 genetic subgroup. The Switzerland/8060 is a 3C.2a2. And so, the 2a2s are what I showed you on those pie charts, the ones that are predominating globally now. The 2a1s are the older viruses, which seem to be dying out.

But just to be clear -- and I want to clear up something regarding a question that Arnold had earlier. If we're just purely trying to understand the antigenic differences of the viruses, the best thing to do is to compare how the circulating viruses

react with self-propagated referenced viruses. And there we see that the Singapore 2016 self-propagated virus covers all the circulating viruses very well, including 2a2. It's just if we take the 2a2 viruses, and ask the same question of them, raising sera to these viruses, they don't cover the other genetic subgroups as well.

So, in the instance that we still have Singapore in our vaccine for the 18/19 season, in the Northern Hemisphere, antigenically, our data says that it should cover all of the circulating viruses well. It's just when you get into the egg-propagated referenced viruses, we see bigger differences. And so, we felt because the 2a2 viruses are predominating globally, and a candidate vaccine virus was available against the Switzerland virus, that it would cover the majority of viruses better than the Singapore egg-propagated vaccine virus would.

DR. GREENBERG: If I could just follow up. The Switzerland 2a2, in your summery, at least for the 2a2 viruses, covered those similar strains well but

not the other subclades. You're less concerned about not covering the other subclades as you would if we were to stick with the Singapore strain?

DR. KATZ: Correct.

DR. OFFIT: Quick question to follow up to that. The ACIP meeting in June, for data presented looking at propagated vaccines in people greater than 65 years old as compared to the standard sort of egg-based vaccine and showed that it was 10 percent better. That vaccine, if I'm correct, is actually down to the trial children who are greater than or equal four years of age. Are there any data on younger age groups, adults or older children, or young children, on this vaccine's ability or how it compares to egg-based vaccine, presumably because it's not -- it's able to recognize these H3N2 strains, that undergo sequence changes during egg propagation, that it appears to be better at least in that one study in that one age group.

DR. KATZ: Right. And that was a relative effectiveness. Yeah. As the cell-based vaccine is

continued to be used in the US, we're setting up some studies this year, although I believe they're mostly in adults; to really try and understand and have panels of sera from individuals that received the cell-based vaccine, to see if we see the same broader reactivity that we see with our ferret antisera. But right now that data just isn't available. But we hope to gather the sera to be able to look at that this year.

And then also to be doing more studies to actually compare, side by side, the vaccine effectiveness in observational studies against egg-based versus non-egg-based vaccines. And they include both the cell-based and the recombinant.

DR. GREENBERG: Thank you.

DR. KATZ: Okay.

DR. EDWARDS: If there are no other questions, I'd like to just go around the list of the participants and have them make any comments or any specific questions that they would like to make before we vote. I'd like to start with Melinda.

DR. WHARTON: Thanks Kathy. This is clearly, as always, a really complex set of data and I appreciate the very clear presentation by Dr. Katz, and the discussion. I don't think I have any additional questions. I'm comfortable with the WHO recommended choices.

DR. EDWARDS: Thank you, Melinda. Sheldon? Sheldon, do you have any comment?

DR. TOUBMAN: Yes. I'm sorry, I was on mute. I do have a comment. I appreciate Dr. Katz's presentation very, very much and also the answers to the questions that were raised. I still have a concern about this question of the trivalent versus quadrivalent. Because, as I understand it, the choice on the Yamagata one versus Victoria, it's -- even though we don't know, everything is at a crapshoot to some degree.

The fact is that the Yamagata is more prevalent now, so we have that as a factor. And then on the other side, you know, Jackie pointed out that a lot of folks were saying, yeah, but there's this

nonimmunity for the Victoria, especially this new strain, so we need to get some immunity out there, so that's a reason for doing that. But then somebody else asked the question, yeah, but we even have immunity for the Yamagata, and the answer is we don't have any data on it. So, then the other question that was raised by somebody else was, well what about the severity of the Yamagata versus Victoria? And what we have there is that we have some hospitalizations for the Yamagata and we have uncertain -- sounds like -- uncertain conclusive data with regards to Victoria.

So, I guess, you know, from my uneducated point of view, just weighing all those things, it doesn't strike me necessarily as the right decision to go with the Victoria. But, you know, I'm uneducated and the other folks on this call, obviously, are intimately more informed than I am; and plus, Jackie, who obviously includes some of the most expert people in the world. And she says that they say this decision. So, I'm not really in a position, obviously, to second guess it but I do have that

concern, that balancing those in the trivalent, I'm not sure I would vote it.

DR. KATZ: Kathy can I just respond to clarify something?

DR. EDWARDS: Please. Yes. Absolutely.

DR. KATZ: Regarding the severity and the relative virulence, I can't say that Victoria is any less virulent in the older adults. I just gave you a snapshot of what we saw this season in the US with B/Yamagata predominating. Quite possible, we'd see the same thing in a season where B/Victoria and particularly a new variant circulated.

I wasn't trying to make any distinction between those two, but just provide you with a factoid of some information that we saw, from our season in the US, which for the B viruses, B/Yamagata predominated. So, of course, we would see more hospitalizations, overall, in that group because they were the predominant B. But there did seem to be a slightly higher proportion in all the adults than we had seen previously.

DR. TOUBMAN: Thank you for the clarification.

DR. EDWARDS: Thank you, Sheldon. Andy?

DR. SHANE: Thanks, Kathy. I appreciate the presentation as well. It was very helpful and very informative. I support the recommendation from the WHO as well. Thanks

DR. EDWARDS: Thank you. Geeta?

DR. SWAMY: Thanks, Kathy. I don't really have any comments. I appreciate all of the data that was presented.

DR. EDWARDS: Thank you. Okay, Paul Spearman?

DR. SPEARMAN: I also appreciate the presentation. I think the complexity of H3N2, especially, was very fascinating and difficult. I can see why they take three days to debate this. I just kind of wonder, in the future, if we don't have more polyvalent vaccine where's there's these dominant subclades that you're trying to predict. I don't have any specific questions regarding that. I think it was very informative. Thank you for the discussion.

DR. EDWARDS: Thank you. Paul Offit?

DR. OFFIT: Yes. I too support the recommendations as offered and appreciate Jackie's presentation. It shows you how live flu is such a moving target. We talk about the universal flu vaccine, we'd just settle for a better flu vaccine. It's just so hard to just capture this virus. I just really want to praise Jackie, that was an outstanding presentation. I actually trained in Walter Gerhard's lab at Wistar, so I have somewhat an appreciation for this. That was great. I certainly support the current recommendations.

DR. EDWARDS: Thank you. Dr. Monto, who has been dealing with influenza for quite a few years, what are your thoughts?

DR. MONTO: Well, you can see why we've gone to quadrivalent. Not so much because there isn't some cross immunity, at least in some populations, but the inability to predict what's going to be coming in the future. I think the biggest worry with Bs is not whether we are predicting the right virus, or not, in the trivalent, but the triple deletion, which is not

covered very well by the B/Victoria.

As usual, an excellent presentation, Jackie. I support the recommendations and would like, even though it may complicate the situation even further, to hear a little more next spring, at the Northern Hemisphere Recommendation meeting, about neuraminidase and DRiP there. Because I think it's one of our low hanging fruits for improving the vaccine.

DR. KATZ: Thanks, Arnold. If I can make a comment. I totally understand. I tried to streamline this report a little bit for the Southern Hemisphere, but yeah, we'll definitely include more neuraminidase for the Northern Hemisphere decision.

DR. EDWARDS: Thank you. Cody Meissner?

DR. MEISSNER: Yes. Thanks, Kathy. As really an amateur of understanding of influenza, each time I hear about it I realize how extraordinary complicated this whole story is. But, first of all I do support the recommendation, and I have just one comment.

As we look at the epidemiology for the maps of the world for each of the three strains that we've

been talking about, the amount of activity, whether it's widespread outbreak, regional outbreak, local activity, sporadic activity, follows the boarders of the country for obvious reasons. But probably the virus, itself, doesn't follow that pattern. It just seems interesting that Brazil, for example, with H3N2, had local activity and I guess it's Paraguay, just south of that, that had more activity. And then Argentina had sporadic activity, looking at the H3N2 maps.

I assume that represents differences in their ability to do surveillance, rather than an actual accurate description of the amount of disease they're seeing in these neighboring countries. And the question, I guess, is should we have more than two influenza vaccines? Should we divide it further by continent rather than Northern Hemisphere and Southern Hemisphere?

DR. KATZ: Do you want me to respond to that?

DR. EDWARDS: Jackie, please.

DR. KATZ: Yes. It is interesting that we do

see -- and I would say the same is true, if you think back, of the Northern Hemisphere in Europe. It was really a remarkable season, overall, where H3N2 dominated so much in the US and Canada, not so much in Mexico. In Europe, the predominance, it was H1 or it was H3 or it was a B; it really varied by country.

And so, in those regions, I don't think we're seeing big gaps in surveillance. And likewise, in the Southern Hemisphere in South America, I think there really is some regionality there. Brazil, of course, most of the country or part of the country is in a subtropical region. So, WHO considers sort of different transmission zones; and you might see different patterns there and the virus circulates at different times of the year.

So, there's a lot of complexity to it. I think there are regional differences for the different subtypes and lineages, it's not only explained by differences in the surveillance capacity. And maybe some of it is more just due to how many visitors they get, you know, the transportation, the climate. Many

different things can play into what is going to predominate in a particular country, in a particular season.

DR. EDWARDS: Thank you. Dr. Levy?

DR. LEVY: Hello. I also support the recommendations. I do have some comments, but I don't know the answer to this. I wanted to know, is there notetaking for our comments and do our comments end up in a public record of some sort?

MS. HUNTER-THOMAS: Your comments are a part of the transcript, which will be posted online, the VRBPAC website.

DR. LEVY: Thank you for that. I again, commend the presentation from WHO and Dr. Katz. Obviously, complicated and enormous amount of work. I do think our discussion illustrates the need for moving forward and perhaps stating the obvious as NIAID has designated, and other federal agencies have designated, improvement in flu vaccine formation and delivery to be key to addressing this global challenge. But the need for greater precision in the

way we approach this entire field. And that precision will come from a lot of direction.

We've alluded to being more precise about which viruses, as they're evolving, we're targeting. There was some discussion, just now, about being more precise about the regions in the world because we might see different circulation in different regions, as was highlighted in today's presentation. But there's also increasing evidence that human populations vary, both between populations and within populations, in a response to a given vaccine.

So, all of this complex information, to me, makes this really a bioinformatics question. And I would hope to see, in the years ahead, more engagement from those who model this in silico, you know, with bioinformatic tools and artificial intelligence tools, as in parallel with the effort to develop better formulations.

One particular population, as a pediatrician, that I focus on are the very young. And we saw that there was some data shown about pediatric and elderly

cohorts, which are helpful. In some cases, those pediatric cohorts were more limited. And I would just put in a plug with the powers that be, and whoever decides this resourcing, that moving forward they fully resource the infrastructure such that robust pediatric data is also included to inform the decisions.

There are many new tools becoming available in vaccinology. And obviously, Dr. Frouchie (phonetic), and others have highlighted the importance of directing those tools towards this huge challenge. And hopefully, in the years ahead those tools will help us do even better.

DR. EDWARDS: Thank you, Ofer. Thank you. Michael Kurilla?

DR. KURILLA: Yes. I concur with the recommendations. The only additional comment I would add is it seems from this discussion that some -- not all -- but some of the discussion could be obviated by moving to a quadrivalent completely replacing the trivalent. I guess I'm curious as to whether that's

more on the manufacturer side or is that a regulatory agency side, country by country specific, as to whether they are able to make that move. It seems that most of the discussion we've had could have just been circumvented by a quadrivalent only question.

DR. EDWARDS: Jerry, do you want to address that question?

DR. WEIR: I think you're right. It does depend a lot on the manufacture and if they're license to make a trivalent or quadrivalent they can do either. I suspect what drives a lot of this is premarketing conditions and market forces. And if the demand is for quadrivalent, that's what they will produce most likely.

DR. EDWARDS: Thank you. Michael, did you have any other comments?

DR. KURILLA: No, I'm fine. Thank you.

DR. EDWARDS: thank you so much. Holly?

DR. JANES: I second the recommendation of Dr. Katz and I really appreciated the comments and questions on the part of the committee that have

helped to clarify the rationale. And I support the WHO recommendation. No further comments from me.

DR. EDWARDS: Thank you so much. David Greenberg?

DR. GREENBERG: Yes. Thank you. And I too greatly appreciate Dr. Katz's presentation. There was a lot of complex information summarized very nicely. I do have a couple of comments and questions.

One is, I must say I'm really struck by the change in the number of viruses submitted and detected for the different virus types by GISRS globally. I mean, you know, particularly when you showed the graph of the data for H3N2. We all know that there was a pretty strong season in the Southern Hemisphere for the H3N2 in our summer months last year, and this year there's almost nothing. So, I'm assuming it's a function of the decreased incidence of disease and decreased circulation in the Southern Hemisphere, not only for H3N2, but all the viruses. So, just a general comment.

A question, I guess, is when I look at these

graphs across the different strains, it makes me realize that much of what you've analyzed for WHO, and now for us today, in VRBPAC, are for the most part strains that are being analyzed from the first quarter of 2018, just because there hasn't been very many viruses isolated during the last three to six months. So, is there any opportunity to increase surveillance programs?

I realize that's a question we can't answer today. But is there any consideration being given to trying to increase the number of strains that can be collected from Southern Hemisphere locations; so that you have a better selection of strains to see what's happening in terms of trends across the different mutations and clades, that are occurring prior to this fall meeting?

DR. EDWARDS: Kathy?

DR. KATZ: To answer your second question first -- well, I think I'm answering both parts really. I think the reduced number, this season, was reflective that there was just a lower level of

activity. Had there been more activity, we would have had more viruses. And since we have a collaborating center in Australia, they are a focal point for data from the Southern Hemisphere. And Australia and New Zealand had an abnormally low season. They barely -- I don't think they did break the threshold of their influenza activity. But there were still hundreds of viruses that they gathered from around the region with the predominance being H1N1.

In South America, again, the numbers typically tend to be smaller. Where the GPRA (phonetic) system is trying to improve the timeliness we've made last year, new recommendations, new guidelines to how many to send, how often to send, what the timeliness needs to be, what the representativeness needs to be. But some of that is limited by the surveillance systems in different countries.

And that is something that WHO is working on and moving towards trying to right-size, if you like -- that's a term we use in the US because we've done that for our US surveillance -- in terms of getting

more viruses in, even if they are not representing the activity levels as much, that we still have enough viruses to characterize within a region. So, we are working on that. But I think the lower number this season just totally reflect the low activity that was seen in Australia, New Zealand, and other parts of the region.

DR. GREENBERG: The other question that I'd just like to touch on for a second is on Victoria. The Colorado, so that's a double deletion, as I understand it, and it reacted well particularly with the double-deletion strains. I did take notice of the cartography graph that there does exists strains from the September 2017 to August 2018 surveillance that, by my uneducated eye or untrained eye, looked to be quite distant. So, even with the selection of Colorado, which is a better selection than the Brisbane, would I be correct in saying that we would still likely have some circulating strains that are not going to react well?

DR. KATZ: Yes. I think that's correct and it

really depends on, as this double deletion is becoming predominant in several regions, whether that is going to continue to all regions. And again, our fitness forecast has predicted that it would eventually replace the older strain, the B/Brisbane-like strains, and that's probably the majority of viruses out there that are not well recognized by a B/Colorado vaccine. We expect that they probably, after, are going to circulate, but the prediction, based on all the available data and the growing emergence of this double deletion variant, is that it will take over eventually. Whether that's totally in the next season, we don't know.

DR. GREENBERG: Thank you and I support the recommendations of the decisions that were made by WHO. That's all my comments and questions. Thank you.

DR. EDWARDS: Thank you, David. I certainly share the comments that Cody made about the complexities of influenza. I think I understand it less the older I get than my earlier years.

I do really applaud the beautiful data that Jackie presented, and also the ability to dissect some of the egg and the cell culture issues. As Paul said, these are going to be really important things that we need to go forward in trying to dissect them and really seeing how they impact vaccine effectiveness in the various populations. I really think that's helpful. And I do support them as well.

VOTING ON RECOMMENDATIONS

Has everyone had a chance to comment on the recommendations? Okay, I think so. Then let's go ahead and vote on the first questions. The question is: For the composition of trivalent 2019 Southern Hemisphere formulations of influenza, does the committee recommend the inclusion of an A/Michigan/45/2015(H1N1) virus, the inclusion of an A/Switzerland/8060/2017(H3N2)-like virus, and the inclusion of the B/Colorado/06/2017-like (B/Victoria lineage).

Because we don't have the automatic voting, then what we'll need to do is just go around the room

and you say either yes or no. Is that correct, Serina?

MS. HUNTER-THOMAS: Yes, that's correct.

DR. EDWARDS: Okay. Good. Let me then start, Melinda?

DR. WHARTON: I vote yes, I support the recommendation.

DR. TOUBMAN: Yes, I support the recommendation.

DR. SWAMY: Yes, I support those recommendations.

DR. SHANE: Yes, I support the recommendation.

DR. SPEARMAN: Yes, I support the recommendation.

DR. OFFIT: Yes, I support the recommendation.

DR. MONTO: Yes.

DR. MEISSNER: Yes.

DR. LEVY: Yes, I support the recommendation.

DR. KURILLA: Yes, I support the recommendation.

DR. JANES: Yes.

DR. EDWARDS: And Dr. Greenberg does not vote, correct?

MS. HUNTER-THOMAS: Yes, that's correct.

DR. EDWARDS: And Kathy Edwards, yes. I think that everyone affirmed the first recommendation.

MS. HUNTER-THOMAS: Yes. If you could hold on one moment. They're going to display the total results on the webcast. However, you guys won't see it unless I share the webcast with you, but we do know it's a unanimous vote of yes.

DR. EDWARDS: Wonderful. Okay, tell me when we're ready for the second question.

MS. HUNTER-THOMAS: Okay, we're ready for the second question, Dr. Edwards. Thank you.

DR. EDWARDS: The second question: For the quadrivalent 2019 Southern Hemisphere formulations, does the committee recommend the inclusion of the B/Phuket/3073/2013-like virus of the (B/Yamagata lineage) as the 2nd influenza B strain in the vaccine.

Okay, let me get my list here. Melinda, would you like to start for us again, please?

DR. WHARTON: Sure. Yes, I support it.

DR. TOUBMAN: Yes, I support.

DR. SWAMY: I support.

DR. SHANE: Yes, I support.

DR. SPEARMAN: Yes, I support the recommendation.

DR. OFFIT: Yes.

DR. MONTO: Yes.

DR. MEISSNER: Yes.

DR. LEVY: Yes.

DR. KURILLA: Yes.

DR. JANES: Yes, I support the recommendation.

DR. EDWARDS: Thank you. And Kathy Edwards, yes, I support the recommendation. Serina?

MS. HUNTER-THOMAS: Okay. If we could wait a few seconds so they can display. And we know that was also a unanimous vote of 12 yes.

DR. EDWARDS: Wonderful. Before we adjourn the meeting, I would like to turn it over to Serina, who will acknowledge two people that will be leaving the committee and I think she wanted to comment.

MS. HUNTER-THOMAS: This is the last meeting for Dr. Ofer Levy. And on behalf of the FDA, on behalf of CBER, on behalf of VRBPAC, we thank you for your service for rendering your keen expertise to this committee. And we greatly appreciate your ability to provide input to the various topics that VRBPAC presents. And we thank you very much for your service.

DR. LEVY: Thank you for the opportunity to serve. Thank you.

MS. HUNTER-THOMAS: And on behalf of FDA, CBER and VRBPAC as well, for Dr. Edwards, we're not quite finished with you, but this is officially your last meeting serving as chair. We would like to thank you, Dr. Edwards, for your leadership of this committee. It has been an honor to serve besides you as the Designated Federal Officer, and we will see you next year.

DR. EDWARDS: Thank you very much and certainly the expertise, quality and scientific input to the committee by the FDA, and also by Serina's good

mentorship and leadership, has been very important. I'm going to miss it as well. Thank you all for a very productive meeting. Thank you, Jackie, thank you, Jerry, for your clear and concise presentations. And I think that if there are no other comments, then I will adjourn the meeting.

MS. HUNTER-THOMAS: Thank you so much, Dr. Edwards, thank you, everyone.

[MEETING ADJOURNED]