UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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149TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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October 4, 2017
1:00 p.m.

FDA White Oak Campus
Building 31, Great Room 1503
10903 New Hampshire Avenue
Silver Spring, MD 20993

MARK SAWYER, M.D.	Acting Chair
KATHRYN EDWARDS, M.D.	Voting Member
HOLLY JANES, Ph.D.	Voting Member
OFER LEVY, M.D., Ph.D.	Voting Member
SARAH LONG, M.D.	Voting Member
PAMELA McINNES, D.D.S., M.Sc. (Dent)	Voting Member
PATRICK MOORE, M.D.	Voting Member
ARNOLD MONTO, M.D.	Voting Member
MELINDA WHARTON, M.D., M.P.H.	Voting Member
SHELDON V. TOUBMAN, J.D.	Consumer Representative
DAVID GREENBERG, M.D.	Industry Representative

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M E E T I N G

(1:00 p.m.)

CAPT HUNTER-THOMAS: Thank you all for joining us. Dr. Edwards is en route, and she will be joining us shortly if she's not on the line already.

So instead of her starting the meeting as a chair, Dr. Mark Sawyer has agreed to be her backup until Dr. Edwards can join us.

Dr. Sawyer, you have the floor.

DR. SAWYER: Thank you, Serina.

Welcome, everybody. Good morning and good afternoon to those joining us all by webcast. I'd like to welcome you to the 149th meeting of the Vaccines and Related Biological Products Advisory Committee.

Today's topic is the discussion on the strain selection for the 2018 Southern Hemisphere influenza season. The Committee members are participating in this meeting via teleconference, and hopefully, everybody has succeeded in logging in. And we're awaiting Dr. Edwards, who will join us as soon as she is able.

With that, I would like to turn it back over to Ms. Hunter Thomas to do a roll call and have the Committee members introduce themselves.

CAPT HUNTER-THOMAS: Thank you, Dr. Sawyer.

So we're going to start with a quick check-in to see if

Dr. Edwards has joined us yet.

Dr. Edwards?

(No response.)

CAPT HUNTER-THOMAS: And when I do call your name, if you are present, Committee members, after you confirm your presence, please state your organization after you confirm your name.

So moving on to Dr. Holly Janes?

DR. JANES: Good morning. This is Holly Janes. I'm at the Fred Hutchinson Cancer Research Center.

CAPT HUNTER-THOMAS: Thank you.

Dr. El Sahly? Dr. El Sahly?

(No response.)

CAPT HUNTER-THOMAS: Okay. Dr. Long?

DR. LONG: Sarah Long here at St. Christopher's Hospital for Children in Philadelphia.

CAPT HUNTER-THOMAS: Thank you.

Dr. McInnes?

DR. McINNES: This is Pamela McInnes, Deputy Director, NCATS, at the NIH.

CAPT HUNTER-THOMAS: Thank you.

Dr. Moore?

DR. MOORE: This is Pat Moore. I'm at the University of Pittsburgh Cancer Institute.

CAPT HUNTER-THOMAS: Thank you.

Dr. Monto?

DR. MONTO: I'm here, Arnold Monto, University of Michigan.

CAPT HUNTER-THOMAS: Thank you.

And, Dr. Sawyer, would you like to state your organization?

DR. SAWYER: Yes. So this is Mark Sawyer. I am a pediatric infectious disease specialist at the University of California, San Diego.

CAPT HUNTER-THOMAS: Thank you.

Mr. Toubman?

MR. TOUBMAN: Sheldon Toubman. I'm an attorney with New Haven Legal Assistance Association in New Haven, Connecticut.

CAPT HUNTER-THOMAS: Thank you.

And Dr. Wharton?

DR. WHARTON: Melinda Wharton. I'm Acting Director of the National Vaccine Program Office.

CAPT HUNTER-THOMAS: And also Dr. Levy, please?

DR. LEVY: Hi, this is Dr. Ofer Levy. I'm the Director of the Precision Vaccines Program at Boston Children's Hospital and Harvard Medical School.

CAPT HUNTER-THOMAS: Thank you.

I'd like to circle back and see if Dr. El Sahly has joined us yet?

(No response.)

CAPT HUNTER-THOMAS: And also check in on Dr. Edwards?

(No response.)

CAPT HUNTER-THOMAS: Okay. Thank you. We'll --

DR. GREENBERG: And Serina, sorry, this is David Greenberg. Can I introduce myself?

CAPT HUNTER-THOMAS: Oh, I'm sorry, Dr. Greenberg, yes, please, by all means.

DR. GREENBERG: Great. Thanks. David Greenberg serving as the Industry Representative and with Sanofi Pasteur. Thank you.

CAPT HUNTER-THOMAS: Thank you, Dr. Greenberg.

Okay. We'll now move on to the housekeeping and followed by the Conflict of Interest Statement.

Welcome, everyone, again to the 149th -- oh, sorry. Excuse me. I also need to do introductions to the most important people here, the OVRR.

DR. GRUBER: Hi, this is Marion Gruber, Director, Office of Vaccines Research and Review, CBER.

DR. WEIR: I'm Jerry Weir. I'm the Director of the Division of Viral Products at CBER.

CAPT HUNTER-THOMAS: And also Jackie Katz, please?

DR. KATZ: Hi, this is Jackie Katz from the Influenza Division at CDC; also, the WHO Collaborating Center for Influenza.

CAPT HUNTER-THOMAS: Okay. Thank you. Okay. Thank you.

On behalf of 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 September 11th, 2017.

The press media representative for today's meeting is Ms. Lyndsay Meyer, and the transcriptionist for this meeting today is Mr. Mike McCann.

I would like to remind everyone to please check your pagers and your cell phones and make sure that they are either turned off or in silent mode.

Committee members, when you're making a comment, being that you are not in the room, please first state your name and speak up so that your comments are accurately recorded for the transcription record.

And I will now proceed to the Conflict of Interest Statement.

The Food and Drug Administration is convening today, October 4, 2017, for the 149th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

At this meeting, in the open session, the Committee will discuss and make recommendations on the safety and effectiveness of the selection of strains to be included in an

influenza virus vaccine for the 2018 Southern Hemisphere influenza season.

The following information on the status of this Advisory Committee's compliance with federal ethics and conflicts 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.

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.

Related to the discussions at this meeting, all members and consultants of this Committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has authorized

FDA to grant waivers to special government employees and federal 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 U.S. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions.

Mr. Sheldon Toubman is serving as the Consumer Representative for this meeting. Consumer representatives are special government employees and therefore are screened for their financial conflict of interest and screened prior to their participation.

Dr. Jacqueline Katz is employed by the Center for Disease Control and Prevention, National 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 is the speaker for this meeting and has been screened for conflicts of interest. She has been cleared to make a presentation at this meeting.

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

FDA encourages all other participants to advise the Committee of any financial relationships that you 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 exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest Statement for the public record, and at this time, I would like to hand the meeting back over to Dr. Sawyer.

DR. SAWYER: Thank you very much, Ms. Hunter-Thomas.

So, again, I would like to announce the topic of today's

meeting, which is the strain selection for the 2018 Southern Hemisphere influenza season. And our first speaker to introduce today's topic is Dr. Jerry Weir, Division of Viral Products, Office of Vaccine Research and Review at CBER FDA.

Dr. Weir?

DR. WEIR: Thank you, everyone.

I'm going to give just a brief introduction and some background to describe why we're here today and then present the questions that we will be asked to vote on at the end of the presentation.

So if you follow the slides that I have put together, the slide number 2 describes the purpose of today's VRBPAC committee discussion. We're here to make recommendations for the strains of influenza A (H1N1 and H3N2) and B viruses to be included in the 2018 Southern Hemisphere formulation of influenza vaccines licensed in the United States.

The next slide. So as a little bit of background for today's committee discussion, the World Health Organization makes recommendations for the virus strains to be included in an influenza vaccine. They do this two times a year, one for the Northern Hemisphere, which is recommendations are made in February or March each year for the following winter season; and then the second recommendation is usually made in September for the next year's Southern Hemisphere influenza season.

Even though the WHO gets together and makes these

recommendations, it's up to each national regulatory authority to approve the composition and formulation of the vaccines in each country. For us, that's VRBPAC provides this recommendation for U.S. licensed manufacturers in February -- and this occurs in February and March for all of the influenza vaccines that are used in the Northern Hemisphere influenza season.

The FDA's CBER approves license supplements for U.S. manufacturers to incorporate these updated strain recommendations. And this updating of the license usually occurs in June to July, before the start of the Northern Hemisphere season.

Back in 2016, there was a U.S. vaccine manufacturer that was approved to produce a Southern Hemisphere formulation for their influenza vaccine, so it is our view that the strain recommendations and supplement approval for the Southern Hemisphere formulation should follow the Northern Hemisphere process. So our meeting today is, in a sense, somewhat of an abbreviated version of the longer, more involved VRBPAC strain selection meeting that we do in February or March for the Northern Hemisphere.

If you go to the next slide, you see the type of data and types of analysis that will be presented. And this will all be presented by Dr. Jacqueline Katz from the CDC and in a sense is a summary of what went on a week ago at the WHO strain

selection meeting. She will present data on the epidemiology of circulating strains. She'll include surveillance data from the U.S. as well as from the rest of the world. As I said, this is summarized from the meeting last week.

She'll also present data about the antigenic relationships among contemporary viruses and candidate vaccine viruses. Some of the data that most of you are familiar with will be things like hemagglutination inhibition tests and virus neutralization tests using post-infection ferret serum; also some HI and virus neutralization tests using panels of sera from humans who have received the most recent inactivated influenza vaccines; and she'll probably also include some antigenic cartography, as well as phylogenetic analysis of the HA and neuraminidase genes.

The next slide describes the previous recommendations for the Southern Hemisphere. This was done about a year ago, and the WHO recommendation was made on September 29th, 2016. And at that point, the WHO recommended that Southern Hemisphere vaccines contain an A/Michigan/45/2015 (H1N1)pdm09-like virus. They recommended an A/Hong Kong/4801/2014 (H3N2)-like virus. And they recommended a B/Brisbane/60/2008-like virus, which was from the B/Victoria lineage. These were for trivalent influenza vaccines.

And then, further, the WHO recommended that any quadrivalent vaccines that were manufactured that would contain

two influenza B viruses would contain the three viruses/strains that I just mentioned plus a B/Phuket/3073/2013-like virus from the other B/Yamagata lineage virus.

We had a VRBPAC meeting shortly after the WHO strain selection, and the Committee recommended that any U.S. manufacturers of Southern Hemisphere formulations adopt the same strains that I just listed.

The next slide. Just to recap what we did at VRBPAC and recommending for the Northern Hemisphere strains back this past February and March -- actually, it was March this year -- there was a WHO recommendation made on March 2nd, 2017, for the upcoming influenza season in the Northern Hemisphere. And at this time, the WHO recommended the following viruses for trivalent influenza vaccines:

An A/Michigan/45/2015 (H1N1)pdm09-like virus. This for the Northern Hemisphere was a change from the previous 2016-17 Northern Hemisphere season, but as you note, it was the same as the 2017 Southern Hemisphere recommendation that I just mentioned in the previous slide.

The Committee also recommended an A/Hong Kong/4801/2014 (H3N2) virus -- this was no change from the previous Northern Hemisphere season -- and a B/Brisbane/60/2008-like virus from the B/Victoria lineage, and this was also no change from the previous 2016-17 Northern Hemisphere.

The Committee also recommended that any quadrivalent

vaccines containing two influenza B viruses contain those three strains, those three viruses, as well as a B/Phuket/3073/2013-like virus from the B/Yamagata lineage.

The U.S. VRBPAC recommendation was made in March, March 9th, 2017.

The next slide shows a summary of the WHO recommendations for the Southern Hemisphere that were just made about a week ago. This was made on September 27th, 2017. And at this time, the WHO recommended that trivalent vaccines for use in the 2017 -- I think that's supposed to be '18 -- Southern Hemisphere influenza season contain the following:

An A/Michigan/45/2015 (H1N1)pdm-like virus; an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; a B/Phuket/3073/2013-like virus from the B/Yamagata lineage; and then they recommended that any quadrivalent vaccines containing the two B viruses contain those three viruses and a B/Brisbane/60/2008-like virus.

The next slide. So the committee discussion today, as I said, will be which influenza strains should be recommended for the antigenic composition of the 2018 Southern Hemisphere formulation of any influenza virus vaccines that are being produced by U.S. licensed manufacturers.

The next slide shows the voting questions. What we tried to do, I hope, is make this fairly simple and a slightly simpler process than we use for the Northern Hemisphere, where

we vote on all four strains. In this one, since these vaccines are not really for the U.S. -- they're for the Southern Hemisphere but made by a U.S. manufacturer -- we thought we would try to make it simple and have two voting questions.

One is for the composition of a trivalent vaccine and in a sense asks you whether you recommend using the three strains recommended by WHO. And that would be Question 1: For the composition of the trivalent 2018 Southern Hemisphere formulation, does the Committee recommend . . . and then these would be the three strains: A/Michigan/45, A/Singapore, B/Phuket.

And then a second voting question that would say: For any quadrivalent Southern Hemisphere formulations, does the Committee recommend including the fourth strain, which in this case would be the WHO-recommended B/Brisbane/60/2008-like virus.

So that's the quick introduction. I'll turn it back over to the Chair if that's okay.

DR. SAWYER: Yes. Thanks very much, Dr. Weir.

Let me just ask if any of the Committee members have any questions about the background material that Dr. Weir has provided?

MR. TOUBMAN: I do have a question. This is Sheldon Toubman. May I ask it?

DR. SAWYER: Yes, please. Go ahead.

MR. TOUBMAN: So in terms of jurisdictionally, this is recommendations for the Southern Hemisphere. The Food and Drug Administration is part of the United States government. So is the jurisdiction over this based upon the fact that there are some territories that are in the Southern Hemisphere or Americans in the Southern Hemisphere? Or is it just based on the fact that the manufacturers are licensed in the United States, and so it doesn't matter where they're selling or where they're using their product?

DR. WEIR: I think your interpretation of it is correct. A couple of years ago, as I said, we were approached by one manufacturer that said that they would like to produce a Southern Hemisphere formulation, and they would like to add that to their license. So if they add it to their license, then we would like to follow the same sort of procedure of getting your VRBPAC input on what they produce even though it is not going to be marketed in the United States.

MR. TOUBMAN: Thank you.

CAPT HUNTER-THOMAS: Are there any other questions before -- thank you, Dr. Weir. Are there any other questions before we move on?

DR. MOORE: Yes. This is Patrick Moore. I was just curious about that last comment. So the Southern Hemisphere vaccine cannot be purchased in the United States at all currently?

DR. WEIR: This is Jerry Weir again. That is my understanding. You would actually probably have to directly ask the manufacturer how they intend to distribute it, but my understanding is they mainly make this for use somewhere else. And just for -- and maybe this won't clarify it. It's not really a traveler's vaccine either. It is just a license formulation of their vaccine.

DR. MOORE: The reason why I'm asking that is we'll see in the next presentation that the antigen change may be important for Northern Hemisphere as well, and I'm just wondering whether this vaccine has the potential to be available for the Northern -- or for the United States.

DR. WEIR: Again, I think the manufacturer would probably have to tell you that, should that situation happen. I actually don't know.

CAPT HUNTER-THOMAS: Okay. Thank you.

Dr. Sawyer, would you like to introduce our next speaker?

DR. SAWYER: Yes. Thanks very much, Dr. Weir, for your background.

And now for the details of the WHO deliberation and the background for the strains that have been selected, I'd like to re-introduce Dr. Jacqueline Katz from the Centers for Disease Control, who's already been formally introduced. So I will just turn it over to Dr. Katz.

DR. KATZ: Okay. Thank you, Dr. Sawyer.

Good morning and good afternoon to everybody. I'll be presenting a summary of the wealth of data that was deliberated on last week in Melbourne, Australia, for the 2017 Southern Hemisphere Influenza Vaccine Virus Composition meeting.

If you'll turn to the next slide, just some details about the WHO system. This is known as the Global Influenza Surveillance and Response System, or GISRS. This system, which includes 6 WHO collaborating centers, about 143 national influenza centers from 113 countries, 4 essentially regulatory laboratories, and multiple H5 reference laboratories, performs year-round surveillance for influenza viruses, both seasonal and novel influenza viruses that emerge from animals.

At the meeting held September 25th to the 27th, last week, the chair was Dr. Takato Odagiri from the WHO collaborating center in Japan. I helped Dr. Odagiri co-chair this meeting. And in total, the nine voting advisors are the directors of the six collaborating centers and three central regulatory laboratories. In addition, there were 24 observers from multiple national influenza centers, H5 reference laboratories, others from the WHO collaborating centers, and ERLs, our academic partners, such as the University of Cambridge, and our veterinary sector partners from OFFLU.

Next slide, please. So this slide shows the different countries, areas, and territories that shared viruses with the WHO collaborating centers during this period, from February to

August 2017. And you can see that most regions of the world were represented.

Next slide, please. This slide gives us the global circulation of influenza viruses for both the Northern Hemisphere season starting around weeks 43, 44 there, shown along the x-axis. And you can see that large peak, first peak, which is the Northern Hemisphere season. Most of the viruses were influenza A viruses, shown in various shades of blue.

And for the Northern Hemisphere season, you can see the very dark blue is not subtyped. The slightly lighter, teal blue color is H3N2 viruses. And then the pale blue, which is really barely visible along the x-axis there, are (H1N1)pdm09 viruses.

So you can see for the Northern Hemisphere season, H3N2 viruses predominated. B viruses are shown in various shades of orange. And so you can see that there -- as we see in many seasons, there was a light peak of B viruses in the Northern Hemisphere.

Moving towards the right-hand side of this graph, you can see a more modest rise in the number of specimens reported to -- received by WHO labs. And for the Southern Hemisphere season, so you can see, again, the majority is H3N2, with much smaller amounts of influenza B and influenza A(H1N1).

Next slide, please. And this just shows proportionally the percentage of viruses by subtypes reported to WHO, most of

them influenza A, and the largest proportion being H3N2, and more equal proportions of the influenza B viruses although, here, there's a large proportion where the lineage, the Victoria or B/Yamagata, is not determined. And about 10% of the viruses were influenza A(H1N1)pdm09. So I'll start with a more detailed description of the (H1N1)pdm09 viruses.

Next slide. And then next slide again. So, overall, the circulation for (H1N1)pdm09 viruses was at a lower level globally, taking second place to H3N2 viruses for the tail-end of the Northern Hemisphere season and for the majority of the Southern Hemisphere season. But you can see a few regions, particularly Mexico and regions in the Indian subcontinent in particular, that had quite a robust H1N1 season. And the H1N1 virus is, in fact, predominated in their season, in countries like India, Bangladesh, Nepal, and the Maldives, for example.

Next slide, please. This is the number of (H1N1)pdm09 viruses detected by GISRS. And you can see, compared with the black line, which is the 2016 season, which was a high H1N1 season, 2017 is quite modest overall. And that's shown by the red solid line.

Next slide, please. So this is what we're now referring to as a mega-tree. This is all of the genetic data available, hemagglutinative (H1N1)pdm09 viruses made available to the GISAID EpiFlu database, which is used by the collaborating centers to compare the genetic sequence data of influenza

viruses prior to vaccine consultation meetings. This is developed by our colleagues at the University of Cambridge.

And the main point is you can see towards the right-hand side of the slide, they're separated out by month starting from January 2016 going up to August 2017. Each little colored bar represents a sequence of a virus isolated and color coded by the region in which it was isolated.

So the main point to make here is that the (H1N1)pdm09 viruses circulating globally still belong to the 6B clade, and the 6B1 subclade of viruses is still predominating globally, with little if any 6B2 viruses reported in this particular period and just a very small number of older 6B viruses being reported from -- a couple from the U.S. and some from Africa.

Next slide, please. So this is a slightly larger tree, although the sequences that are shown here are not proportionally representative of all of the viruses. But you can see just the main trends here. And so the main thing I want to point out, close to the base of the 6B1 portion shown in bold in red is the Michigan/45 virus, which is the vaccine virus that was used in the Southern Hemisphere this season; it's also in the 2017-18 Northern Hemisphere vaccine.

And so most of the viruses -- and these are color coded by the months in which they were isolated, so quite a number from May, June, and July at the top of the tree. You can see that there's not a very large amount of genetic diversity happening

at the moment among the 6B1 viruses, with the exception of the group at the top of the tree, which according to modelers is the most rapidly growing group of viruses. And these viruses contain substitutions at 74R and 295V within the hemagglutinin protein. And some of these viruses are now also having another substitution of S164T. So these are the viruses to keep our eye on moving forward.

Next slide, please. However, when we look antigenically using ferret reference sera made against a panel of different influenza viruses -- and they're shown along the top horizontal bar there across the top of this hemagglutination inhibition table, which I believe this is from the London collaborating center, and then the viruses shown on the right-hand side in red, the corresponding homologous reference viruses against which the sera has been raised. And then below that in black are the test viruses.

So these are the circulating viruses that have been grown in cell culture and are being evaluated for how similar or different they are from the vaccine virus Michigan/45/2015. So if you'll turn your attention to the column highlighted in yellow, that shows antisera raised to the vaccine virus Michigan/45, with a homologous titer of 1280, shown in red.

And then if you look at the test viruses down the lower part of the column, you can see that the titers there all fall roughly almost within twofold -- most within twofold and all

within fourfold of that homologous titer 1280. And that tells us that antigenically, the circulating viruses using this ferret reference antisera are similar to the Michigan/45 vaccine virus.

There's a number of other antisera here, too, some other 6B1 viruses. And generally, they're all showing the same thing. So using ferret reference antisera, we're not seeing a signal for antigenic change.

Next slide, please. So if we take all of the HI data from the five different collaborating centers that produced this data, you can see that in this table we see that all of the collaborating centers show 93% or greater relatedness of circulating viruses to the Michigan/45. And in total, so 95% of almost 2,000 viruses tested are showing antigenic similarity with the Michigan/45 vaccine virus, and only approximately 5% of the viruses are showing -- are yielding, reacting with antisera, giving titers that indicate that they are reacting poorly.

Next slide, please. And so this is shown visually through antigenic cartography, again, provided by our University of Cambridge partners. And here you can see the older vaccine virus, California/7, the new vaccine virus, Michigan/45 in red, and then color coded in blue are the older viruses and in yellow the more recent viruses circulating in late 2016 and 2017. And you can see that they're still forming a tight

cluster around the Michigan/45 vaccine virus.

Next slide, please. So we also test circulating viruses for how well they are inhibited by antisera, or serum, I should say, from individuals that have been vaccinated with the recent vaccines. And here, we have panels from two Southern Hemisphere regions. The yellow is panels from adults and older adults in Australia. And this actually -- sorry -- this data just shows the adult population, but the results with older adults were similar. And then in Peru, we also had a Southern Hemisphere region where we had a small panel of sera from healthcare workers, also younger adults.

And so we've tested these sera against a number of contemporary 6B1 viruses represented by the virus Maldives/446 and South Auckland/2, both egg- and cell-propagated viruses. And in this figure, we're comparing the response that was seen against the reference virus, Michigan/45, grown in cells as representing the vaccine virus. If that post-vaccination GMT, geometric mean titer, of the response to Michigan/45 is set at 100%, then we've compared the proportionate response against all the other viruses.

And so you can see that we're not seeing any reductions. We consider that red bar set at 50%. If we find geometric mean titers that are below that 50%, that indicates that there is a significant difference against the circulating virus compared with the reference vaccine virus.

And as you can see, in this case, for both of the panels, either from Australia or Peru, the contemporary 6B1 viruses did not show -- in fact, they showed geometric mean titers that were similar to the Michigan/45 cell-grown virus. And this data from CDC, and we also performed a similar analysis against the egg-propagated Michigan/45 and saw similar results.

Next slide, please. So, in summary, from February to September 2017, global circulation of (H1N1)pdm09 viruses was generally low. The vast majority of viruses belonged to the 6B clade. And within that clade, the vast majority of viruses belonged to the subclade 6B1.

The majority of recent viruses were antigenically indistinguishable from the current vaccine virus, Michigan/45/2015, using post-infection ferret antisera and HI testing. And then sera obtained from humans that had been vaccinated with the Southern Hemisphere components were all antigenically similar, giving similar geometric mean titers to that seen with either egg- or cell-propagated Michigan/45 viruses.

So I'll move now onto the H3N2 viruses. And as you'll appreciate in a moment, this is a far more complex picture for the H3N2s than what we're seeing with the H1N1s.

Next slide, please. So as I've already mentioned, the H3N2 viruses predominated globally both in the Northern Hemisphere season as well as in the Southern Hemisphere

seasons. And you can see quite widespread activity in many parts of the world.

Next slide, please. The circulation of viruses in 2017 shown in the red bar, these are the number of viruses detected by GISRS. You can see a peak for the Northern Hemisphere in the early weeks of 2017 and another bump around week 27 through 30, which is the Southern Hemisphere. And this is noteworthy because rarely do we see a real bump in the number of viruses for the Southern Hemisphere. The surveillance there is less. But this smaller peak does reflect the robust season that is currently winding down, particularly in places like Australia.

Next slide, please. So this is just a global snapshot of the different clades and subclades circulating at the moment. H3N2s genetically are getting increasingly more complex, as you will see in a moment. But just to focus your attention, the viruses we've talked about for the Northern Hemisphere season, so the older viruses started out in the 3C.3 group. That's shown in red. And as you can see, we see virtually none of those anymore. I think there was one isolated in Asia, but you can hardly pick it up in this pie chart.

We also had the 3C.3a viruses, shown in purple. You'll remember several seasons ago, we had the Switzerland/2013 vaccine virus. That was a 3C.3a virus. And except for North America, where we did still see a small number of these viruses, they also appear to be dying out and very small

numbers detected in other regions.

So the viruses that are still predominating are the 3C.2a clade, shown in the dark orange, and within this clade is the subclade 3C.2a1. And so you can see the varying proportions of these two groups in different parts of the world. Asia and Oceania had approximately equal circulation of 3C.2a and 2a1, whereas Africa saw more 3C.2a, and Europe, North America, and Central/South America had a predominance of 3C.2a1.

Next slide, please. So this just really highlights the complexity of what we're seeing at the moment. So we have within each of the 3C.2a and 2a1 clades that I've been telling you about, we've further subdivided into additional genetic subgroups. And so the 3C.2a1 viruses at the top of this tree and highlighted in the red boxes at the right-hand side of the screen, you can see that there are at least five different genetic groups.

We've called out five genetic groups that we're tracking because we see these having increased in size over the last -- within the last year. But there's different dynamics occurring within each genetic group, and each genetic subgroup is maybe circulating differentially throughout the world. And I'll show you that information in a moment.

But so you can see, we have the group referred to -- so the 3C.2a1s are really the base. Sequence change is about halfway down the tree. You can see a box that says N171K,

I406V. These are the signature changes that occurred as the 3C.2a1 viruses emerged.

In addition, and I know it's hard for you to see this on the tree, most circulating viruses at the moment also have a substitution at 121. And that is defining the majority of the 3C.2a1 viruses. In addition, there is additional subgroups. And I won't call out of all of these different genetic subgroups, but signature changes are highlighted in the boxes.

Similarly, if you look at the bottom half of the tree for the 3C.2a viruses, there are at least three genetic groups. One is represented by this at the bottom, N31S, D53N. There's also a number of additional amino acid changes which are too numerous to talk about in one go.

But you'll see that there's quite a bit -- if you look at the colored bars, there's quite a bit of pink there, and that represents recently circulating viruses from Oceania. So this subgroup predominated in Oceania amongst the 3C.2a viruses but haven't really been seen anywhere else in the world. And it is believed by modelers to not be likely to become more predominant globally.

Then there's the 144K, 121K group and then another group referred to as 131K and 142K. At the very bottom of the tree, there's the 3C.3a group. And as I mentioned earlier, these are really not predominating anywhere in the world right now.

So next slide. So just to highlight the complexity of

these genetic subgroups, this is representing now just taking a snapshot of the 3C.2a viruses. So this is 3C.2as that do not include the 3C.2a1 viruses. And you can see the three different genetic subgroups that I called out in the previous figure, and they're color coded.

And you can see that there's really different proportions of these viruses circulating in different parts of the world, with North America and Asia and Central/South American having the 131K, 142K viruses predominating. But in Oceania, as I mentioned, the 31S group is predominated. And elsewhere, the 121K, 144K has predominated, particularly in Europe and with small numbers also in Africa.

If we turn to the next slide, you can see this gets even more complex, with more colors for the 3C.2a1 viruses. And this is CDC's breakout of the different genetic subgroups. So we've actually broken it down into more than was just included in the previous phylogenetic tree. But you can see again that a lot of the viruses shown in the pale pink that are circulating globally belong to the 92R, 121K, 311Q subgroup, with varying proportions.

For example, in Europe, they saw a different genetic subgroup shown there in the sort of greenish color, and that was the 121K, 13K group. And elsewhere, another group, there's also the 3C.2a1 consensus group, which is all viruses that are the initial progenitors of this clade. So a very mixed and

diverse and geographically distinct picture for circulation of these different genetic subgroups.

Next slide, please. So this is some summary data I'll show you, first of all, and then I'll show you some actual examples of our HI and virus neutralization data. But this is a summary of all the antigenic characterization, first of all, in this first set of tables, looking at how well the circulating viruses are related to the existing vaccine virus represented by the reference cell-propagated virus, Hong Kong/4801-like virus.

And you can see -- I don't think we need to go through all the numbers, but the top part of the table shows the results using the hemagglutination inhibition assay. And you can see there that the vast majority of over 1300 viruses tested are antigenically similar to the Hong Kong/4801-like reference virus propagated in cells. And if we do test viruses using a virus neutralization test, the same is true.

As a reminder, we're using this addition test, the virus neutralization test, because many of the viruses have -- H3N2 viruses circulating globally at the moment have properties whereby it's very difficult or not possible to test them using the hemagglutination inhibition assay. So we have to move to a different type of assay to evaluate them antigenically. And, therefore, we have additional data with the virus neutralization test, far fewer numbers of viruses tested, but

again, a reasonable number when we combine all of the data from the different collaborating centers.

And then, again, overall, by this test you can see -- the similar result is what we see with the HI in that 86% of the viruses were well inhibited by antisera raised to the cell-propagated Hong Kong reference virus. And these data indicate to us that, antigenically, we're not seeing a difference with the currently circulating 3C.2a or 2a1 viruses relative to the reference Hong Kong/4801-like viruses.

Next slide, please. However, we see a slightly different picture when we now compare the circulating viruses to reference viruses that are propagated in eggs. And these are more representative of the viruses that are used for egg-based vaccine production.

Again, the top part of the panel is shown by HI. Overall, you can see that the proportion of viruses that are well inhibited by antisera raised to the egg-propagated Hong Kong/4801-like virus is generally quite a bit lower than what we saw in the previous table. And overall, 51% of viruses tested were similar. And roughly 50% of viruses were antigenically different from or poorly inhibited by antisera raised to egg-propagated Hong Kong/4801-like virus.

And this difference is exacerbated even more in the virus neutralization tests. This is in part due to issues we have with the titers to the egg-propagated viruses in virus

neutralization tests tend to be very high. So the fold differences with circulating viruses that are all grown in cells appears to be even greater.

So in this table you can see when we measure by the virus neutralization test, only about 35% of the viruses tested were well inhibited by the antisera raised to Hong Kong/4801-like egg-propagated viruses. So, taken together, these data tell us that, antigenically, the viruses have not moved on, but there is a difference when we compare the circulating viruses with the reference viruses that represent the egg-propagated viruses that are used in the vaccine.

And this is data -- the next table -- the next slide, please. Okay. So this is, again, a more complex table, an example of HI data, a table shown at CDC. And I'll just highlight a couple of things. As I showed you with the H1N1 data, the ferret antisera are shown across the top horizontally of the table, and the test viruses, the reference viruses and then the test viruses, are shown down the vertical line.

If you just look at the far right hand, you'll see the viruses are also categorized by the HA group, the 3C.2a, 2a1, or 3C.3a that they belong to, and then broken down even further, the signature changes that represent the different genetic subgroups that we've been keeping an eye on.

But the bottom line of this table is if you look at the highlighted numbers in yellow and focus on the fifth column in,

and this is antisera raised to our Hong Kong/4801-like reference virus, Michigan/15, it has a homologous -- the antisera raised to Michigan/15 has a homologous titer of 320. And if you cast your eye down the column, you can see there are a few what we call low reactors, viruses that react with the sera and titers that are eightfold or greater lower than the homologous titer.

And in this table, a number of these viruses are the 3C.3a viruses. And we're seeing, particularly with the CDC data because we had the opportunity to test more 3C.3a viruses, that quite a number of these viruses are antigenically distinct from the vaccine reference viruses. But the majority of 3C.2a and 2a1 viruses, even those belonging to these different genetic subgroups, are antigenically similar to the Hong Kong/4801 cell-propagated reference virus, Michigan/15.

Next slide, please. This is shown again. This is again CDC data. This is now a focus reduction. It's a virus neutralization assay. And if you'll look at the highlighted columns again, this table is set up in the same way as the HI table. And again, our reference antisera to the cell-propagated Hong Kong/4801-like virus, Michigan/15, has a homologous titer of 2560.

And if you look down the column, most of the circulating viruses tested -- and these are viruses from -- a couple from the U.S. but also from South America and Africa and Europe.

And you can see that the majority of these viruses, with one exception down the bottom there, which is a 3C.3a virus, but all the other 3C.2a1 and 2a viruses are reacting at titers that are within fourfold of the homologous titer 2560, indicating that these were antigenically similar to the Hong Kong 4801 reference virus.

However, if we look at the very first column there, it's not highlighted. It says A/Hong Kong/4801. This is antisera raised to the egg-propagated Hong Kong/4801 reference virus. It has a very high homologous titer of 1280. And you can see the majority of circulating viruses are giving -- reacting at titers that are indicating that they are poorly inhibited by this reference antiserum.

And just one more. So next slide, please. So I've included this slide. This is another virus neutralization data. This is by the Melbourne collaborating center. And just to show you some data with the reference virus Singapore/INFIMH-16-0019. It's highlighted there in the red bar. And you can see the homologous titer of this antisera is 1280. And if you look down the list of test viruses here, again broken out by their different genetic subgroups and their clade or subclade, you can see that antisera raised to this new 3C.2a1 virus actually does a very good job at inhibiting the circulating viruses tested.

So next slide, please. So this is a summary of data from

the Melbourne collaborating center. And if you look down the column that says "Antisera against," there's a number of cell and egg pairs. That means these are viruses that have been isolated from the same original clinical material either in cells or eggs. So we have a true pair to compare.

In some cases, we don't have a pair; we just have an egg-propagated virus or a cell-propagated virus. But there's at least six different egg-propagated viruses here that were compared with the Hong Kong/4801 egg-propagated virus. And this is just a subset of the egg isolates that were produced amongst the different collaborating centers. There's at least another five or six that have been evaluated in the same way.

And the bottom line is what we're looking for is a virus whose reference antisera inhibits the circulating viruses at a higher proportion than what we're seeing with antisera raised to the Hong Kong/4801 egg-propagated virus. And you can see, if you look at the horizontal rows here highlighted in yellow, the second one gives the proportion of viruses that were poorly inhibited. So that's the last column that says greater than or equal to eightfold. If you'll look down that column and look against the Hong Kong/4801 egg antisera, you'll see that 39% of the viruses were poorly inhibited by this antisera.

If you look at some of the antisera raised to other egg-propagated viruses, above that, there's a Brisbane/32 egg, 64% were poorly inhibited. If you look further down, there's a

Norway/3806. It's just in white. It's 94% of the viruses tested were poorly inhibited. And so on. Another Singapore virus, GP2646, 99% of the viruses tested were poorly inhibited.

So this is telling us that these representative egg isolates that are being produced are no better than the Hong Kong/4801, and we're really looking for something that might do better than Hong Kong/4801. And so the only virus that's shown in this table -- and it was really true for other viruses that I haven't shown here, but a number of viruses that were generated either at the London collaborating center or worked up at CDC, and none of these viruses behaved any better than the virus shown in blue here, which is the Singapore INFIMH-16-0019/2016 virus, where although it's a relatively small number of viruses tested to date, because it's a recent reference virus, very few, so only 4%, were poorly inhibited, suggesting that this egg-propagated virus is a better match with the circulating viruses at this time.

Next slide, please. So just moving to a bit more of the genetic analysis, this is a simplified phylogenetic tree of the HA gene. And just to show you again, it's like the mega trees we saw before. The 3C.3a viruses that aren't circulating widely are shown at the bottom of the tree there, with Switzerland/2013 being that reference virus and a past vaccine virus.

About a third of the way up among the 3C.2a viruses is the

Hong Kong/4801/2014, which is the current vaccine virus. And then above that at the base of the 3C.2a1 genetic subgroup is this new Singapore/INFIMH-16-0019 virus. And this virus has the signature changes as I mentioned, the 171K and the 121K, representing most of the 3C.2a1 viruses circulating now. In addition, it's got a substitution at 142G.

So next slide, please. So I'm going to move briefly to the neuraminidase. I think this is the first time we have included antigenic data on the neuraminidase, and this is being made available by Maryna Eichelberger and her colleagues at FDA. And they've been able to do some limited antigenic characterization of neuraminidases of recently circulating 3C.2a and 2a1 viruses.

And the bottom line is that they're finding that the neuraminidase is antigenically distinct from the Hong Kong/4801/2014 virus. And I'll show you why that is genetically in just a moment.

But you can read this pretty much the same way you would read an HI, although it's performed by a different assay which measures antibodies' ability to inhibit the neuraminidase activity. It's called an enzyme-linked lectin assay, or ELLA. And it's performed using reassortants that have an irrelevant HA, so we don't get interference from antibodies against the HA.

And so, just briefly, ferret antisera was produced against

either the Hong Kong/4801/2014 virus or a Switzerland/2013 virus. And the main take-home message here is if you look at the homologous titer of the Hong Kong ferret antisera to the Hong Kong/4801/2014 virus at 1280 and then look at the three bottom viruses that are from 2016 and 2017, you can see that there's a greater than -- or eightfold reduction in the titer, suggesting that the neuraminidase of these more contemporary viruses are antigenically different from Hong Kong/4801.

And this is also borne out by some limited analysis with adult sera from humans that received recent vaccines containing the Hong Kong/4801-like vaccine component. And again, these three bottom viruses from 2016 and '17 are showing reduced geometric mean titers compared to the titer of 226 against the Hong Kong/4801 virus.

Next slide, please. So this is a phylogenetic tree. And again, it's a very dense tree, so I know there's no way you can read the individual names there. But the point to make here is the arrow at the bottom that shows the Hong Kong/4801 vaccine virus is at the base of the tree and actually falls within the 3C.3a genetic group whereas the Singapore/INFIMH-16-0019 virus falls within the 3C.2a1 group. So this was something unusual about the Hong Kong/4801 itself, that its neuraminidase was actually more similar to older 3C.3a viruses.

Next slide, please. So, finally, for the H3N2s, we also looked at human serology, so this is showing here post-

vaccination geometric mean titers measured by the hemagglutination inhibition assay from people vaccinated with either the 2016-17 Northern Hemisphere vaccine or the 2017 Southern Hemisphere vaccine. Both of these vaccines contain the Hong Kong/4801-like virus as the recommended H3N2 component.

And here we're looking at the ability of the virus, of test viruses along the horizontal x-axis there to react with the individual human sera from individuals that received the Hong Kong/4801-like vaccine virus. And we're comparing here to the egg-propagated Hong Kong/4801. So that's set at 100% on the far left-hand side of this figure.

And you can see that because most of these are cell-propagated vaccine viruses that are tested, we see a very substantial reduction compared to the reference egg-propagated virus, with everything falling below the 50% mark.

Next slide, please. If we look at this comparison where we compare against the cell-propagated Hong Kong/4801, and that is set at 100%, and that's the smallish bars set at 100 there for the cell-propagated viruses, either Hong Kong/4801 or Michigan/15, you can see that, still, there is a number of cell-propagated viruses, for example, Delaware/32, Washington/16, some of the Singapore viruses there, that are showing -- and a Chinese virus that I won't pronounce because I'll butcher it, a couple of Chinese viruses -- where we're

seeing overall reduced geometric mean titers compared to the geometric mean titers of the cell-propagated Hong Kong/4801-like viruses.

I'll also just call out you can see on the far left there a direct comparison of the Hong Kong -- of the titers we see against the Hong Kong/4801 egg-propagated virus versus the cell-propagated virus. And this is one of our challenges is that the cell-propagated viruses are, in general, giving quite low titers when we do this sort of analysis compared with the reference virus raised in eggs.

So our next slide. So, in summary, I've told you that H3N2 viruses predominated in many countries and caused severe epidemics, for example, in Hong Kong and in Australia in recent months. I didn't show you, but we did discuss at the meeting there were interim Southern Hemisphere vaccine effectiveness estimates provided to the group. And these were quite low, in the order of about 20% for Australia. And this is quite a bit lower than what we've seen for H3N2 viruses even in other Southern Hemisphere seasons. So there was a general sense that for H3N2, the vaccine effectiveness was below par.

The majority of influenza viruses collected belonged to the phylogenetic clade 3C.2a and the subclade 3C.2a1. And when we used ferret antisera raised against cell-propagated 3C.2a viruses, such as the Hong Kong/4801/2014, we saw that most viruses were well inhibited in both the HI and the virus

neutralization test. And this included multiple genetic subgroups within the 3C.2a and 2a1 viruses.

And this data suggested that there's no true antigenic drift amongst these viruses occurring at this time. However, if we used ferret antisera raised to the egg-propagated Hong Kong/4801 virus, then this antisera poorly inhibited many of the viruses tested. In HI, it's close to 50% and well over 50% by the virus neutralization, signaling that there's a problem with the egg-adapted virus.

So next slide, please. So as you know, egg propagation is known to introduce additional changes that can affect antigenicity, and this is particularly problematic, as I've just demonstrated, for the H3N2 viruses. And it's becoming increasingly more problematic with recent circulating viruses.

And so we've found that the ferret antisera raised to a new virus, the egg-propagated Singapore/INFIMH-16-0019, provided broader coverage against recently circulating viruses from both 3C.2a and 2a1 groups compared with antisera raised to the former 3C.2a Hong Kong/4801-like.

And, in addition, sera obtained from post-influenza-vaccinated human serum panels failed to inhibit a number of circulating viruses when we looked at the cell-propagated viruses compared with the cell-propagated reference, Hong Kong/4801-like virus. And I didn't show you the data, but this was also true when we looked at virus neutralization tests.

So next slide, please. So I'll try and wrap this up and talk a little more quickly about the influenza B viruses.

Next slide, please. So, again, although there was fairly wide circulation of influenza B viruses globally in the reporting period, influenza B viruses were invariably subdominant to the influenza A viruses that were circulating in particular regions, mostly the H3N2s.

Next slide, please. And you can see here shown in the red line, which represents the influenza B viruses for 2017, that the number of viruses actually detected by GISRS were lower than what we've seen in previous seasons.

Next slide, please. This is showing data from WHO looking at the proportion of the different lineages, either the B/Yamagata and B/Victoria lineage. The actual numbers are shown in that small table in blue. And as you can see, only a subset of viruses are actually -- we actually have the lineage determination. But we feel that this is probably generally representative of different regions.

And you can see there that the B/Yamagata lineage predominated globally and primarily in Europe, Oceania, and North America, while the B/Victoria was a little less prevalent. But in regions in Asia and Africa, B/Victoria was predominant.

Next slide, please. And so we'll talk about the B/Victoria lineage viruses.

Next slide. And so, again, this is one of the large trees which shows all of the phylogenetic HA gene data that is available at this time in GISAID. Again, we've color coded the viruses by distinct little bars on the right-hand side by the month in which the virus was collected and by the region it was collected in.

All of the B/Victoria lineage viruses currently still belong to the V1A clade, and that's the clade that's circulated for a number of years now. And overall, there's not a lot of genetic diversity, but there's a couple of exceptions that have become notable in this past reporting period.

The first is a group of viruses that have acquired a substitution at 180V. And then you can see them highlighted there. There's a little bar indicating deletion 162/163. These are viruses that really largely circulated in the U.S. in the Northern Hemisphere season particularly at the end of the season. And these are viruses that have actually acquired a sixth nucleotide deletion, which results in two amino acids at residues 162 and 163 being deleted.

Independently, we also saw if you look further up in the tree, there's another very small group of viruses. These are only three viruses, in fact. It's this DEL 162/163/164. This is an independent introduction because these are viruses from Hong Kong. They acquired a different change at residue 180, from an I to a T, and then they acquired a three amino acid

deletion in the HA protein. These viruses, we only have three examples of these, and they have not been seen further.

Next slide, please. So this just shows the global distribution of the B/Victoria deletion viruses. First of all, if you look over on the right-hand side, there's a circle that says 3. There's a triple deletion viruses that were seen in Hong Kong. And even though they had quite a large, robust season, albeit it was predominantly H3N2, these viruses did not appear to be spreading anywhere in the region and were quite localized.

For the double deletions, and these are the ones that are shown in the various shades of pink and red, you can see that the vast majority of these came from the United States, in fact, with small numbers in other Northern Hemisphere regions, a couple in Canada, a few in Mexico, and very small numbers in some Central and South American countries. One virus only was seen in Australia. And a small cluster of five viruses of these double deletions was seen in Norway during the Northern Hemisphere season but nowhere else in Europe or other regions of the world, suggesting that these viruses are really not spreading very widely at this time.

So next slide, please. So this is again antigenic characterization of B/Victoria lineage viruses. This is some HI data from CDC. All of the viruses highlighted in yellow are viruses of the V1A group. So the test viruses are the

circulating viruses. And you can see that compared with antisera raised to either cell- or egg-propagated Brisbane/60 -- this is the far left-hand side -- you can see that these antisera generally react well with the circulating viruses highlighted in yellow. But the viruses that are not highlighted, these are antigens like 14 through 18, these are the viruses that have the double deletion in the hemagglutinin. And here we're seeing eightfold or greater reductions with antisera raised to the reference vaccine viruses, Brisbane/60/2008.

If you look over at the right-hand side of the column, of the table, we have some viruses highlighted in green. And antigens 5 and 6 are our reference viruses that represent -- this is Maryland/15/2016 viruses, one isolated in eggs, one isolated in cells. And when we raise antisera to these viruses, we can see that the deletion viruses now are generally better recognized by this antisera than they are by antisera raised to the Brisbane/60.

However, antisera raised to these viruses, these deletion variants, do not cover the other circulating viruses very well. So the majority of viruses in this table are not well inhibited by this antisera, suggesting that we have this two-way antigenic difference.

Next slide, please. So this is a little more data from the London collaborating center. And they were able to raise

antisera also to a representative virus of the triple deletion viruses from Hong Kong. This is the Hong Kong 269 virus.

If you'll look at the titers that are highlighted in that salmony pink color, these are the homologous titers to the Hong Kong/269 virus, which is the triple deletion virus. And you can see that they give good homologous titers, but the sera are reacting poorly with any other viruses, including a virus below that, the Norway/2409, which is a double deletion.

So this data is telling us not only are these deletion viruses distinct from the Brisbane/60 vaccine viruses or reference viruses, the triple deletion virus is also antigenically distinct from the double deletion virus.

So next slide, please. So the HI data I just talked to you about is presented graphically here. This is the CDC data where we tested a larger number of the double deletion viruses. So you can see that the majority of viruses are still tightly clustered around the red Brisbane/60/2008 vaccine virus, with the viruses in yellow representing the more recent 2016 and '17 viruses, but that there's a sub-cluster of viruses that are more closely clustered around the light blue large dot, which represents the Maryland/15, so this is our reference deletion virus. So you can see very clearly the antigenic difference between the double deletion and the other majority of circulating viruses that fall into the V1A clade.

Next slide, please. So if we look at the data taken from

all collaborating centers and just remember that most collaborating centers had no deletion variant viruses to assess, and if we focus on the right-hand side of this table and look at the proportion of viruses that were well inhibited by antisera raised to cell-propagated Brisbane/60/2008, we see that the vast majority, 91% of over 1300 viruses tested were well inhibited by the Brisbane/60/2008-like reference virus.

In general, there's a lower proportion if we look at the left-hand side of the table and compare with antisera raised to egg-propagated Brisbane/60. The proportion of viruses, it's still a majority, but it's reduced to 66%. And that's because for a couple of collaborating centers, primarily the CRICK, so the London and Australian collaborating centers, their proportions using the antisera that they produced are particularly low.

But overall, if we compare to the cell-propagated reference vaccine virus, the data suggests that these viruses are not -- by and large are not antigenically different, with the exception of the deletion viruses I've mentioned.

Next slide, please. So this is looking at some human serology studies similar to what I've shown you for the influenza A viruses. We had panels of sera from individuals that were vaccinated either with the 2016-17 Northern Hemisphere or 2017 Southern Hemisphere quadrivalent vaccines. So these all contained the Brisbane/60/2008 component.

And you can see when we compare on the left-hand side here, comparing the geometric mean titers of the test viruses compared to the egg-propagated B/Brisbane/60/2008 reference virus set at 100%, and all of the panels are giving titers that are above that 50% reduction, suggesting that the geometric mean titers took different circulating viruses similar to the B/Brisbane/60/2008.

Children's panels in green, there's some that look like they're 0, but they were actually not tested because of the limited amounts of children's sera available in different institutions to test.

So, interestingly, the viruses that gave good geometric mean titers post-vaccination included the double deletion viruses that were tested. And this is shown by the Colorado/6 and the Maryland/15 viruses. And if you look at the far right-hand side of this first figure, it says double deletion egg. You can see that the geometric mean titers of all these viruses collectively are above the 50% line.

So at CDC, we're a little surprised by this because we can see clear antigenic difference using ferret reference antisera. And previously, in the Northern Hemisphere season, in February, we had a virus, a representative double deletion virus grown in cells, the New York/52, and that gave geometric mean titers compared with the vaccine virus.

So we went back and did some additional testing. And

that's shown on the panels on the right-hand side. We're now comparing these viruses compared with the cell-propagated Brisbane/60/MDCK virus set at 100%. But again you can see that the more recent viruses, the Maryland/15 and the Colorado/6, these are all double deletion viruses. The majority of them are giving titers that are similar and are not substantially reduced compared with the titer to the vaccine reference virus.

So next slide, please. Just briefly I'll turn to the B/Yamagata lineage viruses.

Next slide. And here, this is again a very high-level phylogenetic tree that shows all of the data available. And I just really want to point out that the recently circulating viruses, which you can see if you look at the bars on the right-hand side of this figure, the viruses circulating, say, from February 2017 to August 2017, are all in the Y3 clade. So that hasn't changed much. And really there's very limited genetic diversity in the B/Yamagata viruses at the moment. All of the more contemporary Y3 viruses have substitutions at 173Q and 252V, and that hasn't changed from the previous reporting period.

Next slide, please. So just one quick hemagglutination inhibition test. This is from the Melbourne collaborating center. So the Phuket/3073 is the reference virus. This is the cell-propagated, and it's highlighted in yellow. It has a homologous titer of 160. And if you look at all the test

antigens, and these are viruses from New Zealand, Australia, and a couple from Asia, you can see that all of the circulating viruses are well inhibited by antisera raised to the reference B/Phuket/3073 cell-propagated virus.

And this is also true if you look at the column on the left of that, column F. This is antisera raised to egg-propagated B/Phuket/3073. And again, the majority of viruses, with just one exception there or a couple of exceptions, are well inhibited by this antisera, indicating that the circulating viruses are antigenically similar to the B/Phuket/3073 reference viruses representing the vaccine viruses.

Next slide, please. And this is shown with some additional data, which is shown in antigenic cartography. This is HI data from the collaborating center in Tokyo. And you can see, with the big bull's-eye being in red, the Phuket/3073/2013 reference virus and the more contemporary 2016 and '17 viruses, shown in yellow, are generally closely surrounding that red spot, representing the vaccine virus.

Next slide, please. And so, just again showing you the breakout of this data for the different collaborating centers. Again, if you look at the antisera raised to the cell-propagated Phuket/3073 on the right-hand side of the table, we've tested over 1300 viruses, and 97% of them overall were characterized as being Phuket/3073-like. And if we compared

with antisera raised to the egg-propagated Phuket virus, we get a very similar result, with 95% of the viruses being well inhibited by this antisera.

Next slide, please. And finally, looking at the human serology data, this is again individuals that were vaccinated either with the 2016-17 Northern Hemisphere or 2017 Southern Hemisphere vaccines. These are quadrivalent vaccines with the B/Yamagata lineage. And you can see again that we're not seeing any significant trend that any of the circulating viruses are reacting less well or giving -- the human sera is yielding geometric mean titers against the circulating viruses that are similar and not less than 50% compared with the Yamagata B/Phuket reference viruses.

So next slide, please. So, finally, just to summarize the B/Victoria and B/Yamagata lineages, overall they circulated at varying levels and in different proportions in most countries. The B/Victoria lineage viruses predominated in Asia and Africa. B/Yamagata lineage viruses predominated globally and predominated in Europe, Oceania, and the Americas.

The B/Victoria lineage viruses all belonged to the genetic clade 1A. We're not seeing a lot of genetic or antigenic diversity except for the subset -- a small group of viruses with amino acid deletions in the HA proteins. And these viruses were poorly inhibited by ferret antisera raised against the cell culture-propagated reference virus,

B/Brisbane/60/2008, although as I showed you in the map showing the circulation, these viruses really haven't taken off and are not spreading globally at this point.

For the human serology studies, I showed you that the HI geometric means against representative recent B/Victoria lineage viruses were similar to the HI titers against the B/Brisbane/60 reference viruses.

Next slide, please. And for the B/Yamagata lineage viruses, all of the HA genes belonged to the genetic clade 3. There was very limited genetic diversity among the B/Yamagata lineage viruses at this time. And recently circulating viruses are well inhibited by ferret antisera raised against the B/Phuket/3073/2013 reference viruses, representing the vaccine viruses.

Similarly, the human serology studies show that the HI GMTs against most representative recent Yamagata lineage viruses were similar against the cell-propagated B/Phuket/3073/2013 virus.

Next slide, please. So based on these data, as Jerry has already mentioned, the recent consultation made the following recommendations for the 2018 Southern Hemisphere influenza season:

It was recommended for the (H1N1)pdm09 virus that a Michigan/45/2015-like virus be included; for H3N2 viruses, a Singapore/INFIMH-16-0019/2016-like virus be included; and for

the trivalent inactivated vaccine, that the Yamagata lineage B/Phuket/3073/2013-like virus be included. For quadrivalent vaccines that contain two components, they would contain the above or just mentioned three components as well as the B/Victoria lineage virus, B/Brisbane/60/2008-like virus.

Next slide, please. So that wraps up my presentation. I'd just like to acknowledge the huge amount of work that was made by all of the collaborating centers as well as the headquarter staff in Geneva and our other colleagues, the national influenza centers, that play a very important part in GISRS, our University of Cambridge partners, the essential regulatory labs, and in the U.S., our collaboration with the Association of Public Health Laboratories and our USAFSAM partners. Also, at this time we included fitness forecasting from our predictive modelers in Europe and the U.S. And finally, I'd just like to acknowledge all of our staff at the flu division at CDC.

I'll take questions. Thank you. That's it.

CAPT HUNTER-THOMAS: Thank you, Dr. Katz.

DR. KATZ: Okay.

CAPT HUNTER-THOMAS: Dr. Sawyer?

DR. SAWYER: Are you able to hear me?

CAPT HUNTER-THOMAS: Yes, we are.

DR. SAWYER: Great. I would like to, first of all, thank Dr. Katz for, as usual, an amazing ability to take us through a

very complex set of data very quickly and that we appreciate that very much, those of us who don't live in the influenza world on a daily basis. So thank you very much for that.

So, again, let's ask the Committee if there are questions for Dr. Katz?

DR. MOORE: Yes, Mark, I have a question. This is Patrick Moore.

DR. SAWYER: Please go ahead.

DR. MOORE: Jackie, first, I've been on this Committee for 4 years, and you always amaze me by being able to go through this talk, similar talk, extremely complicated, and you do such a good job. And I want to thank you for that.

I want to go, I want to -- I actually have two questions, one about the H1N1, and then the second, a little more elaborate question, will be on the H3N2 vaccine components.

First, I wanted to go to slide 12, which is the H1N1.

DR. KATZ: Right.

DR. MOORE: And it shows the low titer responses from the different centers. And it looks like everything is fine except for CNIC, which is in China. And also, I noticed in an earlier slide, I think it's slide -- oh, it's slide number 7 -- that China is a hotspot, according to this graph for H1N1. So I'm wondering, going back to 12, whether you're worried if there's a Michigan escape -- starting to come out of China, or does that concern you at all?

DR. KATZ: Yeah, thanks, Patrick. That's a good eye. So, first of all, just with respect to slide 7, which is the activity, this needs to be taken with a little bit of -- because China did not report a predominant (H1N1)pdm09 season. The way this is reported, it's reported to WHO by their regional epidemiologists. And so if they see any H1N1 activity, it can be marked as widespread. That means they saw it in many places. It didn't mean for China in particular that the activity was high.

In other regions in Asia that are shown as regional, I would say that they did have a predominant H1N1 season. But yeah, we did all notice that -- now turning to slide 12 -- that there was a slight up-tick of viruses from China. And we're keeping a close eye on this. There was nothing genetically different about these viruses.

So you'll remember that in order that we really believe there's a drifted virus occurring, we want to see both antigenic changes and then signature genetic changes. And so at this point, we haven't seen signature genetic changes, the genetic variability that was -- or diversity that was seen globally was also seen in China. And so there wasn't a lot of evidence that a new genetic group is emerging. But we are keeping our eye on that very closely. Over.

DR. MOORE: Great. Just one real quick question on H1N1, and that's going to slide 10 and, in fact, all of the

phylogenetic analyses. You know, it seems like it would be very helpful if, since you have the virus and you actually got the virus from someone, if some of your centers could try to also identify evidence for serologic, evidence for vaccination, let alone epidemiologic evidence for vaccination so that it would be -- if we knew all of these viruses were in vaccine-positive persons, then that would suggest that there is vaccine antigenic escape rather than just natural drift in transmission, in mutation in the virus --

DR. KATZ: Right, yeah. Understood. And we try and do that in the U.S. and some other countries, but our ability to catch that because these viruses are coming from different surveillance systems compared to -- and although we ask for that information in the metadata that is provided with the virus, we don't uniformly get it unless we're doing, for example, like a vaccine effectiveness trial or something like that in the U.S.

But yeah, your point is taken, and I think we can all try and do a better job on that. Over.

DR. MOORE: Yeah. I mean, it's a tremendous job that you're doing. It's just we might -- that might be one way to put together both the genetics and the immunology.

I wanted to go to slide 23, I think it is.

DR. KATZ: Um-hum.

DR. MOORE: So this is back in March, I abstained from the

Hong Kong antigen. And the reason I think that maybe we're seeing this, it's not that I was really smart on this, but it's just that it was very frustrating to know the low efficacy that seemed to be occurring with the Hong Kong antigen. And it looks like we're seeing that on 23 and 24. And also the differences between the egg-based and the cell line-based virus neuts are pretty striking.

And we now have the Hong Kong-based antigen as our Northern Hemisphere vaccine for the upcoming season for H3N2, and most of the manufacturers are egg-based vaccines. And so do you have any comments? Do you -- is there any way that the approval of the Southern vaccine, which will be changed to a Singapore that's likely to be more efficacious, can be used in the Northern Hemisphere? I know that may not -- you may not know the regulatory aspects of that, but would you at least recommend that?

And, secondly, there is at least one cell-based manufacturer that is using the Hong Kong antigen. Does your data suggest that we might publicly describe that as a vaccine that we as a Committee think might be more efficacious than the egg-based antigen?

DR. KATZ: Okay. Nice easy questions. Thank you.

(Laughter.)

DR. KATZ: So, yeah, first of all, I'd just like to say that the -- so the HI data, it's suggestive of how the vaccine

effectiveness may be, but we actually need studies to determine the effectiveness to really demonstrate that.

So just to back up, in our Northern Hemisphere season, the final results for the H3N2 effectiveness from the U.S. was 34%, and this was in a season where we know we had both 3C.2a and a larger extent of 3C.2a1 viruses circulating. Now, we all agree 34% isn't great, but it is within sort of the average range of the H3N2s at the moment.

So, yes, we're going to have Hong Kong/4801. It's going into people's arms right now. It's hard to say what will happen. We never know what virus is going to predominate in the upcoming season, but if it is H3N2 viruses, it could be that the Hong Kong/4801 vaccine virus that's in the Northern Hemisphere in the U.S. vaccines being administered at the moment will do less well than they did in the past season.

I think -- I don't believe we can make any recommendations to provide the Southern Hemisphere vaccine. I'll defer to Jerry Weir and others at the FDA, but my understanding is that what needs to be administered is a Northern Hemisphere recommendation composition vaccine.

With respect to the cell-based vaccine that is being produced in smaller numbers, I believe around 20 million doses for the U.S. this year, and it's only licensed in the U.S., they are for the first time, the H3N2 component is actually a totally cell-based vaccine virus. It was isolated in cells and

then produced by the manufacturers in cells.

So we don't have direct evidence that vaccine effectiveness would be better. We think it has the potential because of all of the data I've shown you for the H3N2 to provide better protection. But we still really need the data to demonstrate that cell-based vaccines, particularly ones that are totally cell-based like the H3N2 component of the cell-based vaccine this season, is actually better than an egg-based vaccine. And we're in discussions, and we think those studies should be done.

DR. MOORE: Thank you.

CAPT HUNTER-THOMAS: Dr. Moore, I just wanted to confirm for the record, was that you that's been speaking or asking questions for Dr. Katz?

DR. MOORE: One and the same. That's me.

CAPT HUNTER-THOMAS: Okay. Thank you.

For the record, that was Dr. Moore. Thank you.

DR. SAWYER: Are there other questions for Dr. Katz from the Committee --

DR. MONTO: Yes. This is Dr. Arnold Monto.

DR. SAWYER: Please go ahead.

DR. MONTO: Jackie, since we've got 23 and 24 up, I just wanted to ask you about the results from the Tokyo lab, which seem to be an outlier for the egg-based results, low reactors again -- the H3N2 component was less of an outlier for the

egg-based than the -- the cell culture-based than the egg-based.

DR. KATZ: Right.

DR. MONTO: Is there any explanation for that?

DR. KATZ: So the Tokyo collaborating center was the only collaborating center that you can see that they're not listed in the HI data. They're not performing HIs at all. They're only performing a virus neutralization test for antigenic characterization for the H3N2s. And the test that they use is a little different from what the other centers are using. The others are all basing their virus neutralization test on one that was developed several years ago and was previously referred -- or was referred to by the London group as a plaque reduction. We refer to it as a focus reduction.

The Tokyo group are doing what we call a microneutralization assay, the same neutralization assay that we use for our human serology. And typically, in the antigenic characterization, they can get titers, homologous titers that are very high. And so it potentially could skew their results a little more towards showing poor inhibition. And so that's why some of their data could be -- I mean we need to really evaluate that further if it's the difference in the assay, the difference in the viruses they're testing, which are predominantly from Japan, or a combination of things. Over.

DR. MONTO: A further question, Jackie, which you may or

may not know the answer to. The newspapers and some of the publications we look at have been full of the outbreak of H3N2 in Australia. I know part of that was -- part of the mortality was associated with not using antivirals in nursing homes. But is there any evidence that there was further drift in late specimens from Australia?

DR. KATZ: There's no evidence of drift as we define it using -- evaluating circulating viruses compared to a cell-propagated reference virus. They did see -- I mean, part of their activity was due to quite a number of nursing home and other institutional outbreaks primarily in older adults. And they did see vaccine breakthroughs in that situation, but no evidence, additional evidence of antigenic drift. Over.

DR. MONTO: Thanks.

CAPT HUNTER-THOMAS: And the name of the Committee member who just spoke for the record, please?

DR. MONTO: Arnold Monto.

CAPT HUNTER-THOMAS: Thank you, Dr. Monto.

DR. SAWYER: Are there additional questions for Dr. Katz?

MR. TOUBMAN: Yes. This is Sheldon Toubman. I have a question about how you get to the recommendation from the summary that states on slide 54 that B/Victoria viruses predominated in Asia and Africa and B/Yamagata lineage viruses predominated in Europe, Oceania, and the Americas. How do you get to preferring the Yamagata lineage vaccine for trivalent

and only recommending the Victoria in quadrivalent?

And by the way, I have to say that, you know, I'm really, really ignorant. I mean, I don't -- I'm not a medical person at all, so you have to -- in answering my questions, you have to, you know, start from square one. But I guess the basics here are just what's the selection process?

I looked at the maps on slide 42 and 49. And we are talking about the Southern Hemisphere. And I can't quite tell, you know, where it's worse there, but I'm just trying to figure out what the thinking is in preferring the Victoria -- excuse me -- the Yamagata lineage.

DR. KATZ: Right, right. That's a great question.

I think it was twofold. One, that B/Yamagata was still predominating globally. And I think also the fact that we'd had the B/Victoria as the recommendation for the trivalent vaccine in the past year. So individuals that would have been vaccinated in this Southern Hemisphere season would have received B/Victoria. And I think it was felt that it was time to switch over to the B/Yamagata particularly for young children who may be receiving vaccine for the first time. Over.

MR. TOUBMAN: So does that mean that if they're vaccinated from a previous time, that we expect the protective effect to continue for a period of time, for a period of years?

DR. KATZ: Well, it's not for a period of years, but the

individuals have at least seen that lineage before. And we know for the B viruses, there is some broader cross-reactivity between the two different lineages than what we see for influenza A subtypes, particularly in individuals who've probably had natural infection with one or both and then would get vaccinated.

MR. TOUBMAN: Okay. Thank you.

DR. SAWYER: Additional questions?

(No response.)

DR. SAWYER: Okay. Are we ready to move to the Open Public comment, Serina?

CAPT HUNTER-THOMAS: Yes, Dr. Sawyer. Thank you.

DR. SAWYER: Okay. I would like to now turn to the Open Public Comment session and welcome you to that session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of

your travel, lodging, or other expenses in connection with your attendance or participation at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

And I believe we have one registered speaker for Open Public comment, Dr. Megan Polanin from the National Center for Health Research.

Is Dr. Polanin available?

CAPT HUNTER-THOMAS: Dr. Sawyer, Dr. Polanin is not in the room, and so at this point, we can invite anyone else who is available or interested in providing a public comment.

(No response.)

CAPT HUNTER-THOMAS: And hearing none, seeing none, we can then move on to the committee discussion, voting, and recommendations.

But before we do that, Dr. Sawyer, I would like to take a poll again -- I mean, excuse me -- a roll call of the Committee members again starting with Dr. Edwards.

Dr. Edwards, can you hear us?

(No response.)

CAPT HUNTER-THOMAS: Dr. Edwards has been communicating via e-mail, and she may submit her vote via e-mail, which will

be read aloud for the record.

Dr. Janes?

DR. JANES: Yes, I'm here.

CAPT HUNTER-THOMAS: Dr. El Sahly?

(No response.)

CAPT HUNTER-THOMAS: Dr. Long?

DR. LONG: Here.

CAPT HUNTER-THOMAS: Dr. McInnes? Dr. McInnes?

DR. McINNES: Yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. Moore?

DR. MOORE: Here.

CAPT HUNTER-THOMAS: Dr. Monto?

DR. MONTO: Here.

CAPT HUNTER-THOMAS: Dr. Sawyer, I know you're there.

DR. SAWYER: Yes.

CAPT HUNTER-THOMAS: Mr. Toubman?

MR. TOUBMAN: Present.

CAPT HUNTER-THOMAS: Dr. Wharton?

DR. WHARTON: Present.

CAPT HUNTER-THOMAS: Dr. Levy?

DR. LEVY: I'm here.

CAPT HUNTER-THOMAS: Thank you.

Dr. Greenberg, I just want to check if you're present. I know you're not voting.

DR. GREENBERG: Yes, I'm here. Thank you.

CAPT HUNTER-THOMAS: Okay. Thank you.

Okay. If everyone would please stand by, we are going to post the screen with the voting questions.

DR. SAWYER: And, Serina, we'll then have a chance to have discussion around the questions?

CAPT HUNTER-THOMAS: Yes, absolutely. Thank you.

Okay. Dr. Sawyer, I give you the floor again for continued committee discussion.

DR. SAWYER: So I think we've heard a lot of information today as is usual for this meeting and have had some excellent questions already. I'd like to open it up for any further discussion before we vote on these two questions.

MR. TOUBMAN: There is one more from Sheldon Toubman here. Again, since this is so all new to me, what's the basis for determining whether a trivalent or quadrivalent inoculation is going to be provided? Is there -- is that completely out of the hands of recommendations from FDA, and those decisions are made by other entities?

DR. SAWYER: This is Mark. I can comment that the ACIP, which makes recommendations about the use of vaccines, has not stated a preference of quadrivalent over trivalent. I don't know if anyone from FDA would like to further comment?

DR. GRUBER: No, we don't. This is Marion Gruber. We were going to say the same thing, that the United States is

actually the ACIP will make the recommendations on use of the vaccine. We do license the vaccines. We have both trivalent as well as quadrivalent formulations licensed, but we don't, you know, make recommendations as to the use of these products.

MR. TOUBMAN: So how -- sorry -- thank you for that answer --

DR. SAWYER: This is Mark. I just wanted to add one other additional point of information that might be relevant. You know, the proportion of available vaccine that is quadrivalent compared to trivalent has gradually been increasing over the years since the quadrivalent vaccines became available. And I believe this year, approximately 75% of the vaccine that's sold in the U.S. is quadrivalent.

MR. TOUBMAN: And so the purchasers, I guess, of this, they're the ones who are making the decision?

DR. SAWYER: Well, this is Mark again. I guess ultimately the decision is made between the physician and the individual patients based on available supply and perhaps other considerations.

MR. TOUBMAN: Okay. Thank you.

DR. SAWYER: Are there any other discussion points that anyone would like to raise before we vote?

DR. MOORE: Yeah. This is Pat Moore. If I could reiterate some of the comments and concerns that I have for the H3N2, I think that maybe it's -- I know that we're voting on a

Southern Hemisphere vaccine, and it's a little unclear whether this new antigen for H3N2 will be available. I guess this is -- to FDA to -- if we do start seeing a spike particularly in 3C.2a cases that is dramatic in this upcoming winter, then efforts should be made perhaps to think about how we could get a licensed vaccine or a licensed management to try and -- that whether that's the Hong Kong-based cell-derived vaccine or the Singapore antigen as a single antigen.

DR. SAWYER: Are there any comments in response?

DR. GREENBERG: This is David Greenberg as the Industry Representative. The discussion I think that would take place around addressing that topic would be between the manufacturers and FDA. The manufacturing process for influenza vaccines is some months long, and it does depend on some important aspects, such as obtaining reagents for measuring the contents of antigen in vaccines by each of the different manufacturers.

I personally don't know if those reagents are available yet for the new strain. It usually comes along within a couple of months after a WHO and FDA meeting such as this one. So it's unclear whether a vaccine containing the new H3N2 strain would be available for the winter season in the U.S. or Northern Hemisphere. But that's something that would need to be discussed between manufacturers and FDA.

DR. WEIR: Hi, this is Jerry Weir again. Can I just interject one comment related to the last couple of comments in

this discussion?

From a practical matter, it's unlikely that anyone would have a vaccine with the A/Singapore strain available for the Northern Hemisphere. I mean, if you think about it, all of the vaccine is now becoming available like last month, this month, and being used between now and February. This recommendation for the A/Singapore just came out last week, and any manufacturer that wants to start working with it just begins the process now with the anticipation that they would have a vaccine made and formulated sometime next spring.

So I mean we've been through these scenarios before of how late one could change a recommendation, and I don't think I've ever seen a change -- anyone say that something as late as October, now, much less any later, is at all practical to change the vaccine for the Northern Hemisphere season. So I just don't see how that actually could possibly work in just terms of practically making a vaccine.

DR. LONG: This is Sarah Long. I thought that the questioner was thinking about next October, 2018?

DR. WEIR: Well --

DR. LONG: Not this year.

DR. WEIR: This is Jerry again. Remember, we will go through a strain selection process for the Northern Hemisphere in early March of 2018, so we will all revisit this again based on even more data at the time for the next -- not the current

but the next Northern Hemisphere season of '18, '19.

DR. LONG: No, for 2018 northern season, we will select in March.

DR. WEIR: Correct.

DR. GRUBER: Well, yeah, that's correct. The VRBPAC will meet in March of 2018 to make a recommendation as to the components of the influenza vaccine for the '18-'19. This is Marion Gruber, by the way.

Dr. Weir's comments that he just made, however, were regarding -- and this -- that was our understanding that the Committee members asked -- is it feasible to make the Southern Hemisphere formulation that contains the Singapore available sometimes during the current '17-'18 Northern Hemisphere season, should there be need for it. In other words, should, you know, should these strains start to circulate? So that was the comment made in that regard. And that was the question, how we understood it.

Thank you.

DR. MOORE: Let me just rephrase that. No, I actually made two comments. One is that the FDA think about it a little -- this is Pat Moore -- think about this as -- certainly, I understand getting the Singapore antigen out is probably impossible this late in the season, but we do have a licensed cell-based Hong Kong vaccine. And although we don't have vaccine efficacy data for it, I haven't seen any vaccine

efficacy data presented today. All we have are the implications based on both the neutralizations and HI titers and so forth that we have for the different viruses.

But it looks very much like if we base our judgment on a vaccine being efficacious based on the ferret sera data, for example, in the neuts, that the cell-based vaccine should behave much better even with the Hong Kong antigen, and that is a licensed vaccine. I guess the question is can that be expanded if it's a very small production now, 20 million doses; can it be expanded if we're facing a major epidemic of H3N2, which we may not face this winter? Something to at least keep under consideration.

DR. WEIR: This is Jerry again. I see your point, and it's well taken. I actually don't know how to answer it. Part of it would depend, of course, on the manufacturer when you said could it be expanded. So I don't know the answer to that. It's possible. My guess is that most vaccines have already been purchased at this time, but again, I don't know. That might be possible.

But the real question would be would anyone have the data and the evidence to recommend it? And, for example, I don't think the FDA would be making a recommendation like that. It would all be based, theoretically, that it might be working better, and I don't think we'd have any real-time data to know that. So whether someone else, not the FDA, would make some

sort of recommendation like that, I don't know. It would be, again, would not be based on real-time data, though.

DR. MOORE: Fair enough. Thank you.

DR. SAWYER: Okay. Are there other points of discussion that anyone would like to raise? And at least on my WebEx view, I've lost the questions on the screen. I don't know if they're going to be back.

CAPT HUNTER-THOMAS: We're working on it on this end, Dr. Sawyer.

DR. SAWYER: Okay.

CAPT HUNTER-THOMAS: In the meantime, instructions have been sent to the Committee members that have logged into the WebEx with their phone number instead of providing their name. For those that we have just the phone number, if you could see the instructions that Derek has sent so that you can change it from a phone number to providing your name. Thank you.

And the questions are back up.

DR. SAWYER: So as people take a moment to read and follow those instructions, let me again ask if there are any other points people want to make before we actually undertake the vote?

(No response.)

DR. SAWYER: Okay. It sounds like we're ready to vote whenever we're technically ready to vote.

CAPT HUNTER-THOMAS: Okay. So we are going to --

actually, can you put the questions back up, the voting questions back up for me?

Dr. Sawyer, if you could read for the benefit of the Committee the first voting question, and then we will proceed with the vote?

DR. SAWYER: Okay. So the first question we're asked to vote on is for the composition of the trivalent 2018 Southern Hemisphere formulations of influenza vaccine, does the Committee recommend the inclusion of an A/Michigan/45/2015 (H1N1)pdm09-like virus; (b) the inclusion of an Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and finally, (c) the inclusion of a B/Phuket/3073/2013-like virus from the B/Yamagata lineage?

CAPT HUNTER-THOMAS: Okay. Thank you. So, shortly, you will receive the polling questions through the WebEx, and you will submit your vote. Please stand by.

UNIDENTIFIED SPEAKER: How will we do that?

CAPT HUNTER-THOMAS: Please stand by. You'll see it. You'll see it through the WebEx shortly. Okay.

UNIDENTIFIED SPEAKER: Got it.

CAPT HUNTER-THOMAS: The question is up. And if everyone can proceed to submit your vote? Thank you.

MR. TOUBMAN: A quick question. This is Sheldon Toubman. I did not get the instructions, and I'm using a different computer and e-mail address. So when I vote, I just want to

make sure you know who I am.

CAPT HUNTER-THOMAS: Okay. If I don't see your name or recognize your name, what we'll do is I'll call, I'll call you verbally and request for you to respond with your vote.

MR. TOUBMAN: Okay. Thank you.

CAPT HUNTER-THOMAS: Thank you.

DR. LEVY: Point of clarification. This is Ofer Levy speaking. Given that we're -- I'm using a lot of technologies I haven't before and we're hearing both verbal information, seeing slides that are changing, as I understand it, for Question 1, the inclusion is coming up as one of the strains at a time; is that correct?

DR. SAWYER: No. This is Mark. We're actually being asked to vote on the combination of all three, unlike we do typically for the Northern Hemisphere. This was to make this simpler since this vaccine that we're recommending is just for the Southern Hemisphere. So we're voting on the combination of all three strains.

DR. LEVY: But what's showing up on my screen, it just says inclusion of an A/Michigan/45/2015 (H1N1)pdm09-like virus.

DR. SAWYER: Ah, you need a bigger screen. No, I'm not sure what's happening technologically there.

DR. LEVY: Oh, oh, here. Oh, yeah. I just adjusted my screen. Now they all show up. Interesting. Okay, I'm sorry. It sounds very silly, but I've seen mistakes made with this

kind of stuff.

Okay. And also, just another point of clarification, as I understand it, this "package deal" of these three is essentially the WHO recommendation?

DR. SAWYER: That is correct.

DR. LEVY: Yeah. Okay.

CAPT HUNTER-THOMAS: Thank you. Does anyone else have any questions before you proceed to cast your vote?

(No response.)

CAPT HUNTER-THOMAS: Okay. So, please, Committee members, go ahead and cast your vote at this time. Thank you.

(Committee vote.)

CAPT HUNTER-THOMAS: Okay. Does anyone need additional time to submit their vote?

(No response.)

CAPT HUNTER-THOMAS: Has everyone submitted their vote?

DR. LEVY: This is Ofer Levy. I believe I have. It did kind of gray out and seemed like it understood that I clicked submit, but I'm not sure.

CAPT HUNTER-THOMAS: Okay.

DR. MONTO: Yeah. This is Arnold Monto. I think I've submitted it as well.

CAPT HUNTER-THOMAS: Okay.

DR. MONTO: I had the same experience.

DR. LEVY: Hopefully, there are no hanging chads.

CAPT HUNTER-THOMAS: Okay. Stand by, please. Thank you.

(Pause.)

DR. SAWYER: This is Mark. We may have to put Dr. Katz in charge of the voting process because she can dissect complex processes and deliver them easily to us.

DR. LEVY: This is Ofer Levy speaking. I'm seeing a screen now that seems to indicate that 73% voted yes, 27% voted no --

CAPT HUNTER-THOMAS: Dr. Levy, thank you. Yes. We see that screen, and we're going to do individual tabulations here.

So on behalf of Dr. Edwards, who has submitted her vote via e-mail since we cannot hear her, but she can hear us, she has voted -- for the first question, she has voted yes.

Dr. Janes, what is your vote, please? Dr. Holly Janes?

DR. JANES: I'm sorry. Can you hear me now? I voted yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. Long, your vote, please?

DR. LONG: Yes.

CAPT HUNTER-THOMAS: Dr. McInnes, your vote, please? Dr. McInnes?

(No response.)

CAPT HUNTER-THOMAS: Dr. Moore, your vote, please?

DR. MOORE: Yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. Monto, your vote, please?

DR. MONTO: Yes.
CAPT HUNTER-THOMAS: Dr. Sawyer, your vote, please?
DR. SAWYER: Yes.
CAPT HUNTER-THOMAS: Mr. Toubman, your vote?
MR. TOUBMAN: Yes.
CAPT HUNTER-THOMAS: Dr. Wharton, your vote?
DR. WHARTON: Yes.
CAPT HUNTER-THOMAS: And --
DR. McINNES: Serina?
CAPT HUNTER-THOMAS: Yes?
DR. McINNES: This is Pamela McInnes. I did not have the screen where I could do the unmute. I have it now, and I'm confirming that my vote is yes.
CAPT HUNTER-THOMAS: Okay. Thank you very much. Thank you, Dr. McInnes.
And finally, Dr. Levy, your vote, please?
DR. LEVY: Yes.
CAPT HUNTER-THOMAS: Okay. So, to summarize, we have Dr. Edwards, yes; Dr. Janes, yes; Dr. Long, yes; Dr. McInnes, yes; Dr. Moore, yes; Dr. Monto, yes; Dr. Sawyer, yes; Mr. Toubman, yes; Dr. Wharton, yes; and Dr. Levy, yes. So that's a total of 10 yes votes, 0 abstain, and 0 no votes for Question No. 1.
DR. SAWYER: Okay. We're ready to move to Question 2?
CAPT HUNTER-THOMAS: I believe so, Dr. Sawyer. Thank you.

Question No. --

DR. LEVY: Sorry. This is Ofer Levy. I just have a process question. So it sounded like what you talked about was a unanimous yes, but when I looked at the results, I guess what it's reporting is not noes but abstentions? That's why there's a 27% mark? Those are abstentions?

CAPT HUNTER-THOMAS: Yes. I did a verbal vote, Dr. Levy, and the no answers are for individuals that are not present.

DR. LEVY: But no, it means they didn't vote, no? Or no, their vote was no?

CAPT HUNTER-THOMAS: No. We have -- I just gave a verbal tally, and we have 10 yeses from all of the members present, including Dr. Edwards, who submitted her vote via e-mail.

DR. SAWYER: This is Mark.

DR. LEVY: Right, right, but -- this is Ofer Levy. I'm sorry. I'm still trying to determine -- are you aware of any no votes is what I'm asking?

CAPT HUNTER-THOMAS: Correct. We do not have any no votes for Question No. 1, Dr. Levy.

DR. LEVY: Okay. Because the way it comes up on the system, it makes it seem like there were three no votes. Okay.

CAPT HUNTER-THOMAS: Understood, but we have --

DR. SAWYER: All right. This is --

CAPT HUNTER-THOMAS: I'm sorry. Go ahead, Dr. Sawyer.

DR. SAWYER: Well, I was just going to attempt to clarify.

It sounds like the technology, for those of us who could not vote, it may be registering as noes, which is why Ms. Hunter-Thomas went to a verbal vote to make it clear.

UNIDENTIFIED SPEAKER: It doesn't register as noes; it registers as no answer.

DR. SAWYER: Okay.

UNIDENTIFIED SPEAKER: It says yes, no, abstain, and no answer on my screen.

DR. SAWYER: Are there any --

CAPT HUNTER-THOMAS: So please -- okay. Thank you.

DR. SAWYER: Does anyone else need clarification on the voting process, or can we move to Question 2?

(No response.)

DR. SAWYER: Okay. Let's move to Question 2, then.

For the quadrivalent 2018 Southern Hemisphere formulations of influenza vaccines, does the Committee recommend the inclusion of a B/Brisbane/60/2008-like virus from the B/Victoria lineage as the second influenza B strain in the vaccine?

CAPT HUNTER-THOMAS: Thank you, Dr. Sawyer.

So what we're going to do for Question No. 2 is we're going to forego the WebEx, and we're going to take a verbal again. And I will start with Dr. Janes while I await for Dr. Edwards to submit her response via e-mail.

Dr. Janes, your vote, please? Oh, sorry, sorry --

DR. JANES: Yes.

CAPT HUNTER-THOMAS: I'm sorry --

DR. JANES: Yes.

CAPT HUNTER-THOMAS: Dr. Janes, stand by one second while they set up -- forgive me, excuse me.

UNIDENTIFIED SPEAKER: These things work when they work.

CAPT HUNTER-THOMAS: Okay. I have Dr. Edwards. Okay. Dr. Edwards, I have received your vote via e-mail for a yes for Question No. 2.

And now I would like to proceed with Dr. Janes, please?

DR. JANES: My vote is yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. Long?

DR. LONG: Yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. McInnes?

(No response.)

CAPT HUNTER-THOMAS: Dr. Moore, please?

DR. MOORE: Yes.

CAPT HUNTER-THOMAS: Thank you.

Dr. Monto?

DR. MONTO: Yes.

CAPT HUNTER-THOMAS: Dr. Sawyer?

DR. SAWYER: Yes.

CAPT HUNTER-THOMAS: Mr. Toubman?

MR. TOUBMAN: Yes.
CAPT HUNTER-THOMAS: Dr. Wharton?
DR. WHARTON: Yes.
CAPT HUNTER-THOMAS: And Dr. Levy?
DR. LEVY: Yes. And sorry, another process question. It seems for the first question, we did some web-based voting as well, but we're not doing that for Question No. 2?
CAPT HUNTER-THOMAS: Correct, Dr. Levy.
DR. LEVY: Okay.
CAPT HUNTER-THOMAS: We're doing a verbal.
DR. LEVY: Okay.
CAPT HUNTER-THOMAS: Thank you. Thank you.
And I would like to circle back to Dr. McInnes, please, for your vote?
DR. McINNES: Yes.
CAPT HUNTER-THOMAS: Thank you. So I will read aloud for a final count for Question No. 2.
Dr. Edwards, yes; Dr. Janes, yes; Dr. Long, yes; Dr. McInnes, yes; Dr. Moore, yes; Dr. Monto, yes; Dr. Sawyer, yes; Mr. Toubman, yes; Dr. Wharton, yes; and finally, Dr. Levy, yes; for a total of 10 yes votes, 0 abstain, and 0 no, unanimous vote of yes.
Thank you very much for your patience, and if there aren't any other additional questions, Dr. Sawyer?
DR. SAWYER: Yes. Thank you. This is Mark. I would like

to thank the Committee for excellent questions and discussion, thank Dr. Weir for providing us a review of the process by which this information is gathered and reviewed, and again, thanks to Dr. Katz for a clear presentation about the complex data that's used to support the recommendation that we just voted on. So thanks very much.

And I think with that, we can adjourn.

CAPT HUNTER-THOMAS: Thank you, Dr. Sawyer, for standing in as chair. The meeting is adjourned. Thank you.

(Whereupon, at 3:30 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

149TH MEETING OF THE VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

October 4, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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MICHAEL McCANN

Court Reporter