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Center for Biologics Evaluation and Research (CBER)

Vaccines and Related Biological

Products Advisory Committee

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

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PROCEEDINGS (8:30 a.m.)

Agenda Item: Welcome

DR. EDWARDS: Good morning. My name is Dr. Kathy Edwards from Vanderbilt University, and I am very pleased to chair the meeting this morning of the 145th meeting of the VRBPAC. Today our goal will be to arrive at influenza vaccine strains as we will go forward. I would like to start, first of all, by also welcoming the public, but also welcoming our participants and also the audience on the webcast.

I'd like to start with Dr. Weir and if he could introduce himself and we'll go around the table and with our names and our affiliations.

DR. WEIR: I am Jerry Weir. I am the director of the Division of Viral Products at CBER.

DR. KRAUSE: I am Phil Krause, deputy director of the Office of Vaccines. Also, presenting, for Marion Gruber, who is the director, who can’t be here today.

DR. JANES: Good morning. I am Holly Janes. I am a biostatistician. I am at the Fred Hutchinson Cancer Research Center.

DR. EL SAHLY: Hana El Sahly, Baylor College of Medicine. Vaccine Treatment and Evaluation Unit.

DR. ATREYA: Prabhakara Atreya, acting designated federal officer for the Advisory Committee meeting. I am

also the director for the Division of Scientific Advisors & Consultants.

DR. MOORE: Patrick Moore from the University of Pittsburgh, Cancer Virology Program.

DR. MONTO: Arnold Monto, University of Michigan, School of Public Health.

DR. WHARTON: Melinda Wharton, Immunization Services Division, Centers for Disease Control and Prevention.

DR. BENNINK: Jack Bennink, viral immunologist, from NIAID, NIH.

DR. STANEK: Scott Stanek, preventive medicine. Physician assigned to the Assistant Secretary of Defense for Health Affairs, Health Readiness Policy and Oversight.

DR. SCOTT: Cherise Scott, director, Special Programs at the Global Alliance for TB Drug Development. Also known as TB Alliance.

DR. GREENBERG: David Greenberg, University of Pittsburgh, School of Medicine and medical affairs, Sanofi Pasteur. I am the industry representative.

DR. KATZ: Jackie Katz, deputy director of the Influenza Division at CDC and also the director of the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC.

DR. EDWARDS: Dr. McInnes, would you catch your breath and introduce yourself?

DR. MCINNES: Thank you, Dr. Edwards. Good morning. Pamela McInnes, deputy director, National Center for Advancing Translational Sciences at the NIH.

DR. EDWARDS: Thank you. Welcome, everyone. We would like to now have the conflict of interest statement read.

Agenda Item: Conflict of Interest Statement

DR. ATREYA: Good morning. I am Prabhakara Atreya. As I mentioned, I'm the acting designated federal officer for today's Vaccines and Related Biological Products Advisory Committee. I would like to introduce my colleagues, and also make some administrative remarks before reading the conflict of interest statement for the public record.

I would like to introduce our new DFO, Captain Hunter Thomas, who will be in charge of VRBPAC for all the future meetings, and you met Rosanna Harvey, the committee management specialist for the VRBPAC, and also supported by Denise Royster, assisting the meeting today, and we also have our colleague Jeanette Devine, who is the conflict of interest statement preparation and screening officer.

On behalf of FDA/CBER/VRBPAC, we would like to welcome you all for the 145th VRBPAC meeting. Today's

session has one topic that was open to the public in its entirety, the meeting topic is announced in the Federal Registry Notice of January 12, 2017. Members that are participating in person, public is attending in person or watching the live webcast, the FDA CBER media contact is Mr. Paul Richards who is in the audience. If you have any questions with regards to press, he will be available.

And our transcriptionist is Chanda Chhay at the meeting. He is going to be recording all the deliberations and discussions.

I just wanted to mention that when you speak, please press the microphone to talk and switch them off when you have finished speaking. Please speak clearly and loudly into the microphone so that the transcriptionist, the members, public, and those listening via webcast can hear the discussion.

We have an open public hearing session set aside later in the day. OPH speakers, please sign your name and affiliation on the form on the outside the registration table so that we can announce you when the session comes.

And now I will read the conflict of interest statement for the public record. The Food and Drug Administration is convening today March 9, 2017, for the 145th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of Federal

Advisory Committee Act of 1972. At this meeting, the committee will discuss and make recommendations on the strains to be included in the trivalent and quadrivalent influenza virus vaccines for the 2017-2018 influenza season.

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

With the exception of the industry representative, all participants of the committee as special government employees are regular federal employees from other agencies and are subjected to federal conflict of interest laws and regulations. Related to the discussions at this meeting, 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 purpose of 18 U.S. Code 208 their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching,

speaking, writing, patents, royalties, and primary employment.

FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflicts of interest laws and that 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and our regular government employees who have a financial conflict of interest when it is determined that the agency's need of a particular individual's expertise and service outweighs his or her potential financial conflicts of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflicts 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 are not screened and do not vote and do not participate in any closed sessions.

Dr. Cherise Scott is serving as the temporary consumer representative to this committee at this meeting. She is appointed as a special government employee and is a

temporary voting member who will bring consumer perspective to the committee. Consumer representatives are screened for their financial conflicts of interest and are cleared prior to their participation.

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 the unique current or previous financial interests, financial involvement with any firms whose products they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms whose products are known as 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 conflicts of interest statement for the public record. Thank you.

DR. EDWARDS: Thank you very much, Dr. Atreya. We will now begin our presentations. The first presentation will be by Anissa Cheung, regulatory coordinator of the division of viral products at CBER, and she will introduce the topic.

Topic: Strain Selection for the Influenza Virus Vaccines for the 2017-2018 Influenza Season

Agenda Item: Introduction

MS. CHEUNG: Good morning. I am going to introduce the topics of today's VRBPAC meeting, the influenza virus vaccines strain selections for the 2017-2018 influenza season.

So the purpose of today's VRBPAC meeting is to review the influenza surveillance and epidemiology data, the antigenic characteristic of recent virus isolates, serological responses to current vaccines, and the availability of candidate vaccines strains and reagents, and after the committee reviewed the data and at the end of the discussions, the committee will be asked to make recommendations for the strain of influenza A, both H1N1 and H3N2, and the B viruses to be included in the 2017 and 2018 influenza vaccines licensed for use in the United States.

You are going to hear several presentations from CDC and also DoD, and colleagues from CDC will present the

epidemiology of the circulating strains and this will include surveillance data from both U.S. and around the world. You will also hear talks on the antigenic relationships among contemporary viruses and candidate vaccine strains, and the types of assays and also the techniques you are going to hear about include hemagglutination inhibition test using post-infection ferret serum and also the hemagglutination inhibition test using panels of sera from humans receiving recent inactivated influenza vaccines. Also, the virus neutralization test, antigenic cartography, phylogenetic analysis of HA and also NA genes, as well as the vaccine effectiveness.

So there are several key challenges for vaccine strain selections. First of all, vaccine effectiveness really depends on the match between the hemagglutinins of the vaccines also the HA of the circulating strain of viruses, and as you know, the antigenic drift of HA is continuous for both the influenza A and influenza B viruses. However, the antibody of hemagglutinin correlated with vaccines efficacy, and another challenge is the timelines for influenza vaccines productions. The timelines are relatively fixed and usually we have the strain selections in late February or early March. It is

necessary in order to have the vaccines to be available for the subsequent northern hemisphere winter season.

So normally the manufacturer have to begin production of one monovalent strain before the strain selections at risk in order to fulfill the timeframe. Also the available of the reference strain which we also called candidate vaccine virus, which needs to be suitable for vaccine manufacturing. So what it means is the vaccine productions heavily depends on the growth characteristic of the strain used for manufacture.

So if the strain is not growing, you know, in the optimal conditions with enough yield, it will be very difficult, for them, for the manufacturer to grow. And also the strain specific reagents needed for potency determinations is very critical for the potency determinations for both the inactivated and the recombinant protein vaccines.

So I would like to give you a pictorial illustration of the seasonal influenza vaccines production timetable, and you can see starting from the first steps strain selections and then the generation of the reference viruses and the productions of the potency reagent. As you can see, they are all, all the activities are back to back, and any delays of the above steps will have a big impact on

the distributions of the influenza vaccines to the public prior to the influenza seasons.

And the working viruses for the productions of the inactivated influenza vaccines are traditionally isolated from eggs, and the antigenicity are characterized by the WHO collaborating centers. Starting in August 31, 2016, the use of MDCK cell isolated candidate vaccine strain was approved for the manufacturer of the Flucelvax monovalent bulk.

This cell-derived candidate vaccine virus strain is manufacturer-specific and it is derived from two approved WHO collaborating centers. However, the antigenic analysis is performed the same way as performed for the isolated vaccine virus strain. Last of all, the working viruses are approved for quality and safety by the national regulatory authorities.

For the influenza B virus strain, we know that there are two antigenically distinct lineages are always cocirculating in each seasons, and they are represented by B/Victoria/287 and also B/Yamagata/1688, and right now we have both the trivalent and quadrivalent influenza vaccines available in the United States, and currently we have seven quadrivalent influenza vaccines being licensed in the United States.

The current process for selecting appropriate B strain for inclusion in the trivalent and quadrivalent vaccines is similar to the procedure that we use over the years for the trivalent vaccines recommendations. The WHO and the VRBPAC committee will review the data and make recommendations for each formulations, the trivalent and also the quadrivalent.

So I would like to have a quick review of the previous recommendations for the 2016-2017 northern hemisphere influenza virus strain compositions. So a little bit a year ago, on March 4, 2016, we have the VRBPAC strain selections meeting, and at that time the committee recommended the following strain for inclusion in the U.S. 2016-2017 trivalent influenza vaccines. For the H1N1 strain, they recommend A/California/7/2009 H1N1 pdm09-like virus, and there is no change from the 2015-2016 northern hemisphere recommendations.

For the H3N2 strain, they recommended A/Hong Kong/4801/2014 H3N2-like virus. There is a change from the A/Switzerland/9714293/2013 H3N2-like virus vaccines, but same as the 2016 southern hemisphere recommendations.

For the B strain, they recommend the B/Brisbane/60/2008-like viruses, which is from B/Victoria lineage, and there is a change from the B/Phuket/3073/2013-

like virus, which is from the B/Yamagata lineage, but the same as 2016 southern hemisphere recommendations.

For manufacturers producing a quadrivalent vaccine, the committee recommended a second B strain, which is a B/Phuket/3073/2013-like virus from B/Yamagata, and this strain previously recommended for quadrivalent vaccines in 2016 southern hemisphere.

Also, we have another VRBPAC on October 13, 2016, and this is the first VRBPAC for the recommendations for influenza vaccines for the southern hemisphere 2017, and at that time, the committee recommended that the following viruses be used for trivalent influenza vaccines in the 2017 southern hemisphere influenza seasons.

An A/Michigan/45/2015 H1N1 pdm09-like virus, an A/Hong Kong/4801/2014 H3N2-like virus, and a B/Brisbane/60/2008-like virus which is from B/Victorian lineage. It is also recommended that for quadrivalent influenza vaccines containing two influenza B viruses contain the above three viruses and also a B/Phuket/3073/2013-like virus, which is from the B/Yamagata lineage.

So I would like to summarize where we are right now. In a little bit over a week, WHO have the meeting to give recommendations for the influenza virus vaccines compositions for northern hemisphere 2017-2018, and the WHO

recommended that the following viruses be used for trivalent influenza vaccines in the 2017-2018 northern hemisphere influenza seasons is an A/Michigan/45/2015 H1N1 pdm09-like virus, a change from A/California/7/2009 H1N1 pdm09-like virus, but same as 2017 southern hemisphere recommendations.

For H3N2, they recommended an A/Hong Kong/4801/2014 H3N2-like virus, and no change from the 2016-2017 northern hemisphere recommendations. And a B/Brisbane/60/2008-like virus from B/Victoria lineage, and there is no change from 2016-2017 northern hemisphere recommendations.

And they also recommended that a quadrivalent vaccines contain two influenza B viruses, should contain the above three viruses and also a B/Phuket/3073/2013-like virus, which is from B/Yamagata. This recommendation is no change from 2016-2017 recommendations.

As in the previous years, the national and the regional control authorities, they are responsible to approve the composition and formulations of vaccines used in each country.

So at the end of the discussions for today, the committee will be asked to discuss on which influenza virus strain should be recommended for the antigenic composition

of the 2017-2018 influenza virus vaccines in the United States.

So I would like to show you the options for the strain compositions for the 2017-2018 trivalent influenza vaccines. For influenza A(H1N1), there are two options, either recommend an A/Michigan/45/2015 H1N1 pdm09-like virus or recommend an alternative H1N1 candidate vaccine virus. For H3N2 influenza A, also have two options, either recommend an A/Hong Kong/4801/2014 H3N2-like virus or recommend an alternative H3N2 candidate vaccine virus.

For influenza B in the trivalent influenza vaccines, it has three options. One is recommend a B/Brisbane/60/2008-like virus from B/Victoria lineage, or recommend an alternative candidate vaccine virus from the B/Victoria lineage, or recommend a candidate vaccine virus from the B/Yamagata lineage.

So for the options for the quadrivalent influenza vaccines for the second B strain, it also has three options. The first one is recommend inclusion of a B/Phuket/3073/2013-like virus from B/Yamagata lineage or recommend an alternative candidate vaccine virus from the B/Yamagata lineage. The third option is recommend a candidate vaccine virus from the B/Victoria lineage.

So before I finish my introductions, I would like to fresh up the slides for the questions the committee will

be asked to vote on at the end of the discussions. Those are the two questions for the composition of the trivalent 2017-2018 influenza vaccine virus in the United States. Does the committee recommend the following options, and also another question is for quadrivalent 2017-2018 influenza vaccines in the United States.

This is the end of my presentation. Thank you.

DR. MCINNES: Could you please remind me of the vaccines sold in the United States, what proportion of it is trivalent and what proportion of it is quadrivalent?

MS. CHEUNG: So basically, right now we have, I would say, it's like eight licensed influenza vaccines, and seven of those they have quadrivalent formulations, but the actual number exactly how many of those are trivalent and how many of those are quadrivalent, I'm not really sure. Jerry, do you have any idea?

DR. KATZ: Based on the information that CDC was provided by manufacturers at the start of the season, it's estimated that about 60 percent of the available doses for this past season were quadrivalent, and that has been increasing over the last few years.

DR. MONTO: In all the recommendations, the statement of like is included. Who makes the decision about what is like the recommended virus and what is unlike the recommended virus, number one?

Number two, how are decisions made about those that are producing cell culture based vaccine and, number three, how is the decision made about sequences used for those who are actually making vaccine in insect cells now?

MS. CHEUNG: I think for the like virus questions, I think Jackie will be the best person to respond.

DR. KATZ: The WHO collaborating centers perform antigenic analyses. What we refer to as a one-way test where a particular virus is tested using antisera of the reference virus, for example Hong Kong/4801. A two-way test is when that sera from that particular virus is also raised and we look in two ways whether the virus is similar, for example, again to a virus like Hong Kong/4801. So the answer is it's the WHO collaborating centers that determine what's like and what is not like.

DR. MONTO: What about the cell culture-based vaccine production?

DR. KATZ: Right, so currently two collaborating centers, the CDC and the Melbourne collaborating center in Australia, are producing isolates from the qualified manufacturers cell culture, MDCK cell line, and those viruses are again antigenically tested, compared with the reference vaccine like virus, and then antisera are also raised to those vaccine viruses. I think it was mentioned

earlier that this is similar to the analysis we do for egg-based vaccines. The third question?

DR. MONTO: How are the sequences determined for -- because if the question is are these egg-derived sequences, or are these -- how are the sequences determined?

DR. WEIR: Actually, the sequence is not a direct part of the decision. It's our antigenic likeness is based on hemagglutination inhibition test at this point, not sequencing.

MS. CHEUNG: Are you asking about the insect-derived vaccines? I think for the insect-derived vaccines, we are based on the sequence of the working virus.

DR. MONTO: Cell based or egg is what I'm asking.

DR. WEIR: Cell-based, if we're talking about flu block, that is not based on a sequence. That is a derived reference strain, a candidate vaccine strain that matches antigenically to the like recommended strain. For the recombinant, the manufacturer produces a sequence, and they run it by us in the supplement update and typically -- I mean, it's a fairly limited amount of data, but we have matched it to usually the reference strain of the egg-derived virus, but on the other hand, I have to tell you in the last year we have also considered the wildtype strain too as being acceptable.

DR. MONTO: That is what I was wondering.

DR. EDWARDS: Karen, would you like to introduce yourself?

DR. KOTLOFF: I am Karen Kotloff. I am a pediatric infectious disease specialist at the Center for Vaccine Development, University of Maryland School of Medicine.

DR. EDWARDS: Thank you very much.

The next presentation on U.S. surveillance will be by Dr. Lisa Grohskopf, who is a Captain in the U.S. Public Health Service and Associate Chief for Policy and liaison at the Epidemiology Prevention Branch in the Influenza Division at the Centers for Disease Control and Prevention.

Lisa?

Agenda Item: U.S. Surveillance

DR. GROHSKOPF: Good morning. I am going to present a brief update on U.S. influenza surveillance but also an update on interim vaccine effectiveness estimates for the United States from the U.S. flu VE network.

So we'll start with surveillance. The data that are presented in the next series of slides come from CDC's FluView report, which is issued weekly. These data come from the week 8 report, which is for the calendar week number 8, the week ending February 25.

The first two slides cover virologic surveillance, and the data for these are basically reports related to influenza positive test results that are reported to CDC weekly from approximately 100 public health laboratories and approximately 300 clinical laboratories via either the national respiratory and enteric virus surveillance system or WHO collaborating laboratories located throughout the United States. This first slide summarizes the data for the clinical labs. By and large, the clinical labs don't subtype flu As. So we are looking at untyped As.

We have the calendar week on the X axis, on the left-hand Y axis we have number of positive specimens, which is represented by the lines in the graph, and on the right, by the colored bars and the percent positive specimens on the right Y axis as represented by the lines.

Overall, you can see that the flu viruses that predominated were As. We do see an uptick in the Bs in recent weeks of reporting. Just pointing out for the percent positive specimens that we have overall percent positives, the solid black line up top, has leveled off somewhat in recent weeks.

If we look at the As, that's the next line down, the dotted yellow one, a bit of a decline in the percent positive for As, but this is somewhat matched by an uptick

in the percent positive for Bs as you can see in the bottom line.

So this slide summarizes the same data from the same sources, except it's from the public health laboratories. One difference here is that because the public health laboratories typically or often are testing specimens that are already tested in a clinical laboratory, the percent positive parameter doesn't carry as much meaning. So it's not represented here.

By and large, public health laboratories do subtype As and determine lineage for Bs. The predominant color for all of these weeks thus far has been red, which is flu A(H3N2). There's relatively little AH N1 pdm09. Those are in orange and probably not terribly visible on the slide. They are there but very small. There was an uptick in Bs in recent weeks, and those are represented in the green at the bottom.

This slide summarizes results for genetic testing for flu viruses submitted to CDC. There were total since the beginning of October for the 2016-2017 season of 1,247 tested, 154 AH1 pdm09s. I believe 772 H3s, and 321 Bs.

For the H1N1 pdm09 of the isolates, the 154 that were tested, 100 percent were the HA gene was genetic group 6B.1. For influenza A(H3N2), 96 percent the hemagglutinin

gene was a genetic group 3C.2a. For 4 percent, it was 3C.3a.

For the Bs, among the Victoria specimens, 100 percent were V1A and among the Yamagata specimens, 100 percent were Y3.

Next antigenic characterization results. There were a total of 766 viruses antigenically characterized among the H1N1 pdm09s, all 112 were antigenically characterized using ferret post-infection antisera as A/California/7/2009-like, which is the H1N1 component of the 2016-2017 vaccine. Three hundred and eighty-seven of 399 or 97 percent of the A(H3N2) isolates were antigenically characterized as A/Hong Kong/4801/2014-like. The H3N2 component of the 2016-2017 vaccine.

B/Victoria lineage, 123 of 134, 92 percent antigenically characterized as B/Brisbane/62/2008-like, which is included in both the quadrivalent and trivalent vaccines for 2016-2017, and finally B/Yamagata lineage, all 121 that were antigenically characterized were B/Phuket/3073/2013-like, an influenza B virus included in the quadrivalent vaccines for the current season.

Moving on to two slides on illness surveillance. This first one is outpatient ILI visits. This comes from the U.S. Influenza Like Illness Surveillance Network, or ILINet. Week of surveillance is on the bottom of the chart

on the X axis, percent of visits for ILI are on the Y axis. This network consists of approximately 2,800 outpatient facilities that report each week the percent of outpatient visits that were for an ILI diagnosis, defined as fever of 100 degrees or higher and sore throat or -- I'm actually forgetting the last parameter there, I apologize.

We have a number of seasons represented on this slide. The 2015-2016 season is represented in red with the triangles. That's the current season. For the most recent week of reporting, the percent was reported as 4.8 percent, which is above the baseline of 2.2 percent still for this season. So still seeing activity in ILI for this season.

This is hospitalization data from FluSurv-NET. Hospitalization data is reported overall and by age groups. It's cumulative data. So the lines will continue to go up over the course of the season. Week of surveillance is on the X axis and the rate of hospitalizations per 100,000 population is on the Y axis.

Overall, considering all age groups as of week 8, the overall incidence of hospitalization for confirmed flu was 39.4 for 100,000 population. The highest hospitalization rate goes for 65 and older for whom it is 180 per 100,000 population. That's the highest group for hospitalizations for this season.

The last two surveillance slides summarize mortality data. This first one is information on pneumonia and influenza mortality from the National Center for Health Statistics. This information is compiled from death certificate data, and this is current as through February 11 and March of -- it's for the week ending February 11 as was finalized on March 2.

There is something of a backlog in death certificate data. So these figures do sometimes change during the weeks after they are initially reported, hence the two dates.

For the week ending February 11, the overall proportion of deaths reported due to pneumonia or influenza ICD diagnostic codes was 7.8 percent, which is just above the epidemic threshold of 7.5 percent.

Last surveillance slide, this is pediatric deaths associated with confirmed flu. This is again several seasons worth of data, starting with 2013-2014 on the far left. For the 2016-2017 season thus far, a total of 40 deaths have been reported, including six in the most recent week, week 8.

Summary of the U.S. season. Influenza A(H3N2) viruses have predominated during this season. There has been a recent increase in influenza B activity in the recent past few weeks. So far influenza activity has

overall been moderate and may have at this point peaked nationally. The circulating strains are similar to those contained in the 2016-2017 vaccine.

DR. EDWARDS: Thank you, Lisa. Are there questions? Perhaps I can start. Do you have an idea overall of the overall vaccination rate this particular year?

DR. GROHSKOPF: We just recently have gotten a preliminary read on that that was discussed at ACIP. There are data from the National Immunization Survey that -- this is still early and preliminary and the figures do tend to change over time, but we were able to say at ACIP that overall at least for pediatric coverage, which we focused on because it was an issue because of the LAIV discussion, that as of the end of December, the coverage at least in pediatrics was similar to that of the previous season. It was around 50 percent.

We anticipate that those figures change over time because data continues to be collected through the season, and that was only through December.

DR. MONTO: How did that break down in terms of the lack of availability of live attenuated vaccine? Because there was concern that pediatric vaccinations would drop because of that.

DR. GROHSKOPF: Overall, for the pediatric age group, it was 50 percent, I believe, compared with 51 percent for the same period of time last year. My memory is that for individual age groups -- and again this was all very preliminary -- there wasn't a difference among the various age groups within the pediatric population compared with the previous season. But I expect we will be hearing more about that as time goes on.

DR. MOORE: In your P&I graph, it looks to me that flu rates this season have not been -- or at least flu mortality has not been tremendous this year. We are doing pretty well for that. But if you go back to your ILI slide, where you compare different years for influenza-like illness, it looks like we are actually having a fairly sizeable rate of influenza that may not be caught by the vaccines. So I'm wondering does this mean that we are seeing a high rate of influenza but a low rate of mortality, or should we interpret one graph differently from the other in terms of the surveillance data?

DR. GROHSKOPF: That's a really good question. I think it's a little difficult sometimes, oftentimes, to draw parallels between the systems because the sources of data that are used are just so different. The National Center for Health Statistics data does run off basically death certificate reporting, which has its attendant

limitations to it, and in this case, what we are getting with the ILInet is data directly from providers basically reporting their proportions of ILI visits as a total function of total outpatient visits. So I think I would hesitate to draw a comparison simply because the data sources are so different.

DR. MOORE: What is your opinion on what the flu rates were this year compared to previous years? Are we having an elevated rate of influenza this year, or not?

DR. GROHSKOPF: Well, all seasons are different in terms of their severity. They can be different from one season to another in terms of the segment of the population that is most severely affected. In recent seasons we have had some seasons, for example, where hospitalization rates were greater, for example, among 50 through 64-year-olds than we would have anticipated.

Things do change, and it's hard to form a stable opinion about the severity of flu. I think just looking at this ILI graph, we had by this account a relatively mild season during 2011-2012. This one, you know, seems at least for ILI activity somewhere comparable between 2014-2015 and 2015-2016, but it's going to be different. It's going to be different each year.

DR. MONTO: Just from the view of the CDC-sponsored vaccine effectiveness network, there has enormous

variation between sites in terms of occurrence. Seattle has had a rather severe outbreak whereas other parts of the country have not, and I think that will all come out in the wash as the numbers come through. But it has been a very uneven, uneven influenza season this year.

DR. BENNINK: Are the majority of the H3s, are they 2A.1s, in the country?

DR. KATZ: I'll talk about that, but yes, they are.

DR. JANES: Are there any data at CDC or elsewhere as far as you aware about morbidity and mortality by types of types, lineages?

DR. GROHSKOPF: For the National Center for Health Statistics data, we don't get that for the pediatric mortality data, they do attempt to gather as much clinical information about those cases as possible. I don't recall the overall number for the 40 for this year yet. Among the six that reported during week 8, there were two H3N2s, one H1N1, two unsubtyped and one B. But that's just one microcosm from one week worth of data.

They do attempt to get as much information as possible, but it sometimes takes a few months to get -- probably the virus type comes earlier, but other clinical information comes much later.

DR. EDWARDS: So Lisa, do you want to then go ahead and present the interim VE data?

DR. GROHSKOPF: These slides were presented at ACIP roughly two weeks ago and were prepared by Dr. Brendan Flannery and Jessie Chung, whom I am very indebted to for lending them to me.

The U.S. flu VE network includes five sites. We have Group Health in Seattle, Baylor Scott and White in Texas, Marshfield Clinic in Wisconsin, University of Michigan in Michigan, and University of Pittsburgh in Pennsylvania.

Briefly to summarize the methods, enrollees are outpatients aged at least 6 months or older, with acute respiratory illness or cough, acute respiratory illness symptoms with cough of 7 days or less duration. For this period for this season, the dates of enrollment were November 28, 2016 to February 4, 2017. I'm going to emphasize February 4 is still early, and they are still collecting data. So these figures may change.

The design is a test-negative design in which involves comparing vaccination odds among influenza positive RT-PCR positive cases with RT-PCR negative controls. So everybody is ill, but they are classified as cases or controls based on their flu results.

Vaccination status is defined as receipt of at least one dose of any 2016-2017 seasonal flu vaccine according to medical records, immunization registries, and/or self-report. VE is calculated as 1 minus the adjusted odds ratio times 100 percent. Things that are adjusted for include study site, age, self-rated general health status, race, and ethnicity, and the interval in days from onset to enrollment, as well as calendar time.

For interim results, thus far as of February 4, a total of 3,144 persons were enrolled at five sites. There were 744 or 24 percent that were RT-PCR positive, 76 percent were RT-PCR negative. The breakdown by virus type here is in the pie chart: 80 percent were influenza A(H3N2). Influenza A(H1pdm09) and also B/Victoria account only for 1 percent of the total, 7 percent were unsubtyped, and 11 percent were B/Yamagata.

This chart summarizes the number of enrolled participants by week with the RT-PCR result and also the percent positivity by week of onset. I just want to draw attention to the percent positivity which is in the -- it is summarized by the line that goes across the graph. This was still having an overall general trend upward as of February 4. So I mention that only because, again, it was February 4 and we may continue to see more positive

specimens coming in. So again, these numbers may yet change.

So interim adjusted vaccine effectiveness against medically attended influenza for the season as of February 4 from this study. For any influenza A or B virus overall across all age groups, adjusted VE was 48 percent with a 95 confidence of 37 percent to 57 percent. As we get into the different age groups, once we split into age categories, we of course have a lower number in the denominator and fewer cases. So consequently get some variability and also some widening of confidence intervals.

VE ranges for 19 percent in the 18 through 49 age group, to 58 percent in the 50 to 64 percent age group. Statistical significance is there for 6 months through 8 years and for 50 through 64 and for 65 and older.

For this table, we have the data summarized by virus type. Again, because pdm09 accounted for 1 percent, as did B/Victoria, we are really only able to report A(H3N2) and B, and for B we can't break down by age group, because the numbers are so small.

For A(H3N2) overall adjusted VE was 43 percent, confidence interval 29 percent to 54 percent. Again, looking at the individual age groups for H3N2, there is some variability in the point estimates. For influenza B

overall, 73 percent with a confidence interval of 54 to 84 percent.

In summary, interim results for the 2016-2017 season through February 4, 2017, indicate vaccine effectiveness overall of 48 percent against medically attended influenza. This interim estimate is similar to that seen in previous seasons when the vaccine was well matched to circulating influenza viruses.

Significant protection against circulating influenza A(H3N2) and B viruses, which were predominantly B/Yamagata, was observed. We're not able to calculate VE against H1N1 pdm09 or B/Victoria, due to the small number of cases. Again, enrollment is continuing. We anticipate that there's a good possibility numbers may look slightly different by the time the season ends and the final data are compiled.

Two brief comments. One on VE against influenza A(H3N2). We saw a value of 43 percent here as just mentioned. This is roughly similar to VE against H3N2 in previous seasons with good antigenic match. For example, 2011-2012 and 2012-2013 were both at 39 percent. A meta-analysis of test-negative VE studies by Belongia, et al, came up with a figure of 33 percent. The VE against A in this meta-analysis against A(H1N1)pdm09 and B viruses tended to be higher. A(H3N2) viruses have required more

frequent vaccine updates, as we know from past seasons. Candidate H3N2 viruses also tend -- have a greater propensity to have antigenic changes after adaptation in eggs.

Another thing that's an active area of thought at this point is repeat vaccination. The flu VE network investigators have been going back and looking at prior season vaccination, and it does seem that prior season vaccination is a significant effect modifier in most seasons. The point estimate for the current season, for example, current season only vaccination, will tend to be consistently higher than the current plus prior season. There generally are overlapping confidence intervals, but it does tend to be higher current only as opposed to current plus prior.

There is some evidence also for residual protection from the prior season vaccination consistently for B and for H1N1 pdm09, sometimes for H3N2. This is a complex issue that is an actively evolving area of research.

This slide I can't read the whole thing, summarizes the flu VE network investigators at the sites and at CDC who I want to acknowledge, and I also want to acknowledge folks in our branch and division who compiled this data and put it together. Thank you.

DR. EDWARDS: Thank you, Lisa. Questions? Jack, did you have a question?

DR. BENNINK: I'm going to go to the effectiveness or something like that. It's a little bit off the strain selection, but it applies to effectiveness. Last year, I think, in August, your committee put out recommendations not -- did not recommend live attenuated. Is that going to happen again this year, or how are you thinking about that?

DR. GROHSKOPF: That is an area of ongoing discussion at ACIP. We did have an update on that topic at ACIP two weeks ago, and I would anticipate there's probably going to be another discussion at ACIP in June, but at this point, I wouldn't be able to predict what the decision would be.

DR. BENNINK: On that topic, do you have any advice or things like that for this committee or for the FDA or anything else in terms of that?

DR. GROHSKOPF: I can't think of specific advice with regard to strain selection, I don't know if Jackie can.

DR. EL SAHLY: Is the receipt of trivalent versus quadrivalent a variable that you look at in terms of vaccine effectiveness? Especially as it pertains to B, I guess.

DR. GROHSKOPF: It has not been analyzed at least in the current session that I know of, although the -- and I don't know actually for this season yet what the proportion of quadrivalent versus trivalent received in the population was. They are still compiling that, and again, it's something that may change as the season goes on. But for the 15-16 season, last year, the estimate was that 66 percent of the doses given were quadrivalent.

DR. EL SAHLY: So the data is collected as to who received what in terms of vaccine effectiveness, comparing the trivalent to the quadrivalent as it pertains to the --

DR. GROHSKOPF: They do collect data on the vaccine. It is in general not possible to compare different vaccines for example. It was actually only relatively recently that they were able to start comparing LAIV and inactivated. We have so many different vaccines.

DR. KOTLOFF: I have a question about the effect modification from previous season vaccination. So is that seen if it's the same vaccine in the previous year and the current year? And also how have you looked at it the other way around, that if it's the same vaccine, and you have last year's vaccination, but not this year's vaccination? Do you have any sense of what the effectiveness of that is for this year's flu?

DR. GROHSKOPF: For this year's I don't know. I think it ends up being something of a difficult thing to study, because some seasons they change, some seasons they don't, and there are three different viruses to compare. By the time they get down to running these types of comparisons, particularly if we have a season like this season, as you probably notice, and I think Dr. Monto alluded to, there are not a lot of cases. The statistical difficulties of doing that kind of analysis get troublesome in terms of lower numbers and much wider confidence intervals that are harder to interpret.

I don't know specifically any information that can answer the question you are asking exactly, though. It's something that they are continuing to analyze.

DR. EDWARDS: Lisa, I think -- and perhaps the numbers are too small, but it is sort of curious that the age group that you would think would have the most robust immune response, being 18 and 49, actually has the lowest vaccine effectiveness. So is that a matter of numbers or is that a matter of these people are just not as hardy as we were, or what's the story?

DR. GROHSKOPF: I wish I had an answer for that. I mean, I do think that at least some of the variability has to do with the numbers, particularly once we sub out by age category, and we have had seasons where for one reason

or another efficacy has been greater or less and there have been theories posited about what that particular age group experienced before in terms of exposure to flu or to vaccine. But I don't have an answer.

DR. BENNINK: Maybe you answered this, but are there enough numbers that you could tell whether there was a difference, whether the exact previous year they were immunized or not?

DR. GROHSKOPF: Oh, you mean for that age group, whether they received vaccine the previous year? I don't know. I think that that information probably exists. I don't know that it has been done, and I don't know the answer to the question.

DR. MOORE: So the vaccine efficacy, I am a little worried about the H3, the vaccine strain is not recommended to be changed this year. The vaccine efficacy is not very good, which it generally isn't for H3, but the issue is -- and so we can't expect that next year it's going to be any better. At best it's going to be much -- it's going to be the same, and if there is an expansion of a clone that is not fully recognized by the Hong Kong strain, then it is going to be presumably much worse.

So now changing the strain recommendation would be at least largely dependent on how well it worked in this part year, and that's the reason why I'm asking the

question. Do we have -- do the ILI cases, charts, that you showed indicate that we had a high level of flu activity or should we be looking at the influenza mortality, which suggests that we are having a relatively low level of influenza mortality this past year?

So that would suggest that at least we are doing something reasonably well with the Hong Kong strain and we might not want to change it, but if we are actually seeing a lot of influenza occurring this year, then there's a lot more reason for trying to find a better strain selection for the H3 virus.

DR. GROHSKOPF: I think one of the difficulties with the mortality other than the pediatric, the all ages mortality, the health statistics, and with the ILInet data is that it's not necessarily confirmed flu. So we are dealing with on the one hand ILI activity which could be other viruses, which will have their own seasonal patterns that may vary from one season to the next and on the other hand, we have death certificate data where we don't know that that was confirmed flu either. It's basically ICD-9 diagnostic codes.

So, many of which are not completely flu-specific anyway. We don't have test results for those folks, for example. So I think it's difficult to draw very firm inferences from that, for those reasons.

DR. EDWARDS: Thank you very much, Lisa.

Our next speaker will be Dr. Jackie Katz. She will present world surveillance and virus characterization. She is the deputy director of the Influenza Division and director of the WHO collaborating center for Surveillance, Epidemiology, and Control of Influenza at the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention.

Jackie?

Agenda Item: World Surveillance/Virus Characterization

DR. KATZ: Thank you. So this morning I am going to present to you pretty much the information that was presented in the WHO information meeting to industry last Thursday in Geneva, and this is a summary of the influenza type A and type B global surveillance and virus characterization that was discussed at the three-day vaccine consultation meeting.

So just to remind you, this is the global influenza surveillance and response system, is a WHO network which comprises six WHO collaborating centers, over 140 national influenza centers, four essential regulatory laboratories, and a number of H5 reference labs. So we met from February starting on February 27 last week to review all the data.

I was the chair of the three-day meeting, and the nine advisors shown here from the WHOCCs and ERLs are the individuals who make the final decision, but all the data is reviewed and discussed by a large body including 24 additional observers from various WHO laboratories, as well as the veterinary sector, because we also address zoonotic influenza virus activity and make recommendations for candidate vaccine viruses, but obviously that is not part of my talk today.

So I will just start by showing you what the season looked like globally. These are numbers of specimens that were processed each week by different laboratories within GISRS and reported to WHO. So you can see here the tail end of the last season starting here, climbing quite quickly, and this indicates at the end of 2016 represents several regions that had quite early activity, and then the rest of the season shown here in red in 2017. So quite a robust season in terms of number of viruses but perhaps not quite as high as our previous season.

And I think you have this in your handouts. This again is WHO data, and now breaking down where available the different influenza A subtypes and type B virus information, and if you'll focus on this sort of in between bright bluish teal color, you can see that there was a lot

of activity of H3N2 in many regions of the world, followed and virtually very little H1N1 pdm09 activity, except in a few regions, such as late season in Mexico and South America, and again, this is data from September to February. So some of this reflects the end of the southern hemisphere season, but even in the end of the southern hemisphere season in, for example, in Australia, you can see there was quite a lot of H3 activity.

Again, this is just showing the epidemiological curve of the global circulation, and again, as Lisa pointed out from the United States it was largely an H3N2 season, with a little of B, and the season has stretched quite long. This is as of week 6.

And again, just another representation where you can fully see the viruses reported to WHO through their FluNet system that almost half were H3 viruses, very few H1N1 pdm09s, and a much smaller proportion of influenza B viruses.

Shown here is all the different countries that contributed viruses for our antigenic and genetic surveillance from the period of September through February. So you can see we've got a fairly good global representation, but obviously still some gaps in surveillance.

So I'll begin with our data on the H1N1 pdm09 viruses, and again, these are viruses submitted to the WHO collaborating centers and national influenza centers from September 2016 through February 2017. As we have heard earlier, there wasn't much H1N1 pdm09 activity globally in this period. These maps show the maximum activity during that period in the given countries, and you can see with a few exceptions, like South Africa, India, that had some widespread activity, there's mostly sporadic local activity globally for H1N1 pdm09.

So this is a phylogenetic tree of the hemagglutinin gene of H1N1 viruses, and this is all data that was available prior to the consultation meeting last week. That is submitted by the collaborating centers as they perform genetic characterization, as well as some national influenza centers. All the data goes into a global database called GISAID, and this allows the collaborating centers to rapidly pull out and analyze that data.

This just shows you by region. It's color coded by region. So each one of these little bars represents an HA sequence. There's a time series, and I know you can't read this, but if you'll just focus on the last several columns here, that is the period September through January, and you can see that there really wasn't a lot of activity,

but most of it is the 6B.1 subclade or clade of viruses, and I'll just remind you, so for the last couple of seasons, we have had two H1N1 pdm09 subclades circulating, the 6B.1 and the 6B.2. So in this period, very little 6B.2, and what was out there was 6B.1.

The other thing I just want to highlight is that this tree in general is pretty straight. It's not moving to the right, which would suggest that the viruses are changing genetically, and so this is also demonstrated here. If you are following along on your handouts, I've switched up the order just slightly for some of this genetic analysis, but this is just again to emphasize that in most regions of the world, there was predominating 6B.1 subclade of H1N1 viruses, with very little 6B.2, a couple of viruses in Oceania and in Asia, and Africa still has a little bit of the oldest 6B viruses, and we typically see that the African continent is somewhat behind in terms of viruses, but everybody else throughout the world has pretty much switched to 6B.1.

And if we take a look at in a little more detail at a condensed phylogenetic tree of the hemagglutinin gene, you can see the breakout within the 6B clade of the 6B.1 and the 6B.2 viruses, and again, there's not a lot of genetic diversity happening in the 6B.1 viruses right now. Just to orient you with what you're looking at here, these

are names of viruses. The color codes indicate the months. So the orange and pink are the most recent viruses from December and January, the blue and green are slightly older, October, November viruses.

Also the virus that was still the vaccine virus in the 2016-2017 vaccine for the northern hemisphere, as you know, was the California/7 shown here, and then the Michigan/45/2015 virus which is a 6B.1 virus, was recommended for the 2017 southern hemisphere vaccine, and that was considered a slight update to represent the viruses, the genetic viruses, that were circulating as well as some data that we obtained with antigenic differences as we could see through human serum, and I'll focus on that again in a moment.

So the only changes we are seeing is there's a small cluster here. These are mostly U.S. viruses, and they have three key substitutions at 205, 183, and 166, but many of our colleagues around the world are not seeing these viruses yet, and they still just represent a small proportion.

If we look at the neuraminidase gene, again the phylogenetic breakdown, the viruses fall into the 6B.1 and 6B.2 groups, and again there isn't a whole lot of genetic diversity that we are seeing there.

But if we consider the California/7/2009 vaccine virus and compare it with the more recent 6B.1 reference virus, Michigan/45/2015, we can see -- and this is a three-dimensional structure of a monomer of HA. Shown here are the different antigenic sites in the head of the molecule, and shown over to the right, the red areas indicate where amino acid changes have occurred in the 6B.1 viruses, and so we know that these viruses have accumulated substitutions in both antigenic site SB and in antigenic site SA, which the more recent change at 162, which affects glycosylation for the 6B.1 viruses. And there's also changes in site CA for the H1N1 viruses.

This is a slide I showed you back in October, and it's a way to remind you of the additional analysis we did for H1N1 viruses back for the September meeting, and which contributed to our change in the vaccine virus recommendation and the move to Michigan/45. So what we had done in that analysis last year was to take our panels of pre- and post-vaccination adult human sera from individuals that received the vaccines through from 2010 to 2016 and all of these vaccines included the California/7/2009 component.

So all of these individuals were vaccinated with California/7, and we looked specifically at adults because of some literature that Scott Hensley and others had

developed in terms of finding a certain middle age group that they felt weren't responding to the California/7 virus as vaccine virus and making antibody responses to more contemporary viruses.

So we looked at adults and characterized their potential priming history based on the year that they were born, and based on their profile of their pre- and post-vaccination response to historic former seasonal H1N1 viruses, and we could determine three different profiles. We could determine individuals that were likely primed with USSR/77-like viruses, and they had two different phenotypes. One group shown down here, when they were vaccinated with California/7 made robust responses to the vaccine virus, and then to all other viruses, including different 6B.1 viruses.

But there was a subset of the population that, although they responded to California/7, they failed to make antibody that cross-reacted with the more contemporary 6B.1 viruses, including the Michigan/45/2015 virus shown here.

So last, for the September vaccine consultation meeting, we and a couple of other groups used pooled sera from individuals with this phenotype as well as this phenotype and were able to discriminate by the HI assay some differences with the currently circulating viruses,

and that's shown here in this H hemagglutination inhibition assay, and just to remind you how we set these assays up and what this is telling us, we have a number of reference viruses including the California/7/2009 viruses propagated in eggs or cells, and these represent the vaccine virus, and then other contemporary circulating viruses.

Across the top here we have reference ferret antisera raised to these reference viruses, and the top panel tells us how well this antisera reacts with its homologous virus, which is highlighted here in red. Then we have a series of test viruses from circulating viruses we have just isolated, and we look at how well these viruses are covered by the ferret antisera in the HI test.

Shown in yellow are the antisera raised to egg or cell propagated California/7/2009, and you can see that the titers that we get with the circulating viruses are very similar to the homologous viruses, suggesting that these viruses are all similar to the California/7 vaccine reference viruses.

Similarly, if we use ferret antisera raised to our reference 6B.1 virus, Michigan/45/2015, you can see the same thing, that we have high homologous to the egg and the cell propagated viruses, and these antisera react well mostly within twofold, occasionally within fourfold, of

that homologous titer, again suggesting that the viruses are well covered by sera to Michigan/45.

If we look over here now in the pink, we have highlighted the post-vaccination human serum pool that we are using, and so these are individuals that have received the trivalent or quadrivalent vaccines over the years, and they make robust responses to the California/7 vaccine component, but when we look at their responses to 6B.1 circulating viruses, we can see most of these are at least eightfold or greater reduced, suggesting that at least in the subset of adult human sera, we can discriminate that there is an antigenic difference with more contemporary 6B.1 viruses, compared with the California/7 vaccine virus.

And if we look at this by antigenic cartography, and this is done by our colleagues at Cambridge University, here they have both the California/7 vaccine virus represented in blue, the Michigan/45 represented in red, and because this data is derived from our HIs with ferret antisera, we are not seeing any difference. The 2016-2017 viruses are all clustering very tightly around either one of these viruses, just as earlier viruses also did.

So in summary, this was the tables that we always put together for the different collaborating centers, and their analysis. So here I have both the similarity with the California/7/2009 vaccine, as well as the

Michigan/45/2015 vaccine component which is recommended for the 2017 southern hemisphere, and you can see that we are getting very good antigenic similarity, indicating that these viruses have not moved on and that Michigan/45/2015 antisera covers all of the viruses that we analyzed very well.

We also look at in a different analysis, we use human serology, using contemporary panels of pre- and post-vaccine sera. So these are panels of sera, and there were two sets of different panels, and the different laboratories use different panels. So for the data I'm about to show you, this was data from CDC and other groups that used a U.S. panel of pediatric, adult, and elderly sera, sera from Japan from adults and elderly, and from a UK adult population, and you can see that all of these vaccines contained the California 07/2009 component.

So if we look at -- we're color coding here now by the different panels -- this is just the adult sera, and we're comparing the responses to the cell-propagated California 07/2009, which is shown over here. So we're setting that response at 100 percent, and then we're asking for each of the other more contemporary circulating viruses representing either the 6B.2 subclade or 6B.1 viruses how well the antibody that is raised to California/7 covering these different viruses.

And you can see with the exception of the U.S. panel that most of the viruses are covered quite well. One exception is a 6B.1 Montana 2016, and that virus represents that small genetic group that we're seeing in U.S. at the moment, but not seeing anywhere else, and it's really not the predominating virus, but we used it as a vaccine antigen or a circulating virus antigen in this study.

Using the U.S. sera, and we had very robust responses in our U.S. panel such that we had a very big window to discriminate the different reactivities, if we look at the U.S. sera we are seeing reductions to the 6B.2 and the 6B.1 Michigan/45 cell-propagated and then Indiana 21/2016 cell-propagated 6B.2 virus, but that wasn't as evident in the other panels of sera that we looked at.

So in summary for the H1N1s, activity was generally quite low globally in the period September 2016 through February 2017. And the vast majority of viruses were 6B.1 and the 6B.2 subclade was really detected at only a very low level.

The majority of recent viruses were antigenically indistinguishable from the current California/07/2009 and Michigan/45/2015 vaccine virus components if we used ferret antisera in the HI tests. However, we saw the same phenomenon we saw back in September where if we used a panel of human serum from adults that likely were in that

middle-age group that had experienced USSR 77 as their priming H1N1 virus, then we could discriminate antigenic differences with the contemporary circulating 6B.1 viruses.

And if we looked at post-vaccination geometric mean HI titers, we saw in some adult and pediatric sera tested that there were reductions to some of the contemporary 6B.1 and 6B.2 viruses, but this wasn't universally seen, and it was overall less pronounced in most of the panels we looked at.

So moving on to the H3N2 viruses. As we've already heard, there's a lot of activity in the period September 2016 to February 2017. Widespread activity in North America and parts of Europe and Asia and even regional outbreak activity at the end of the southern hemisphere season in Oceania.

Again, we're looking at a phylogenetic tree of the hemagglutinin genes. These represent all of the viruses that we had available to us, all the sequences we had available to us, prior to the consultation meeting, and you can see that, again, each colored bar represents a sequence from a virus in a particular region, and now I want to point out that this tree as we often see for the H3s, is moving to the right, and you see that there's a lot of genetic subgroups, a lot of little clusters forming here.

The predominance of viruses were 3C.2a viruses globally, and we also saw what we're now referring to as the 3C.2a1 subclade, and these were actually, as you can see, from the period September through January, quite predominant, although there were still some 3C.2a activity, but much less 3C.3a activity.

And just to look at this in a slightly easier way, you can see this is the different regions by month of detection. And you can see the breakdown here, the 3C.2a in the dark orange, the 3C.2a1 in the light orange, so if you look at the pie charts down the bottom, you can see that that paler orange 3C.2a1 is really in many regions overtaking the 3C.2a's.

So in Europe and North America, and most of this is U.S. data, you can see about two-thirds of the viruses were 3C.2a1 and a little over a quarter or so of the viruses or one third of the viruses were 3C.2a. At the tail end of the southern hemisphere season in Oceania, they had a late 3C.3a burst as we did in the prior northern hemisphere season, and in Asia and Africa, there's still more 3C.2a viruses. So particularly in Asia it's still about 50/50 3C.2a compared with 3C.2a1.

So if we look in a little more detail at the hemagglutinin gene and what we're seeing. So the 3C.2a1 viruses are a subset of 3C.2a's, and they are characterized

by having mutations in the HA at amino acids 171, 406, and 484, the latter two being in the HA2 region of the molecule. And you can see that there are several subgroups forming. In addition, many of these viruses now have acquired a change of 121 K, and this upper cluster now is the group that is actively forming different genetic subgroups. In particular we're seeing additional changes at 140 and one change at 135 K which involves a potential loss of a glycosylation site.

And you can see that a couple different places here. So these are the ones we're keeping our eye on, and I'll focus on the change at 121 K with the 135 K substitution in some of the antigenic analysis.

If we look down at the 3C.2a's and of course our Hong Kong/4801 vaccine virus is down here at the base of the 3C.2a viruses, you can see that again there's two major subgroups forming, shown in this phylogenetic analysis. There's a group that has substitutions at 121 K and 144 K, and another group that has substitutions at 131 K and 142. So it's a very dynamic and diverse genetic landscape of H3N2 viruses at the moment. There still was some 3C.3a activity, but as you saw from that pie chart, we really didn't see the burst of 3C.3a activity that we were concerned about at the end of last season. It was truly a 3C.2a and a 3C.2a1 season in the United States.

Again, there's a little bit of genetic diversity going on in the neuraminidase gene, but essentially the viruses fall out into these same clades and subclades that I've already described.

And this is really complicated but how we're trying to look at this is by month, from September through January, what is the frequency of these different genetic groups. And I'm just going to focus on a couple of things here. For the 3C.2a viruses, you'll remember I just called out the group that had changes at 131 and 142 shown in the orange, and the group that had changes at 121 and 144 shown in the purple.

So you can see from September that these two lineages have really -- these two clusters of genetic groups have really taken over the 3C.2a's. The 3C.2a1's are much more heterogeneous. We've got many different groups and I just highlighted the three groups that we're really keeping our eye on in the previous tree, and the only thing I'll point out here -- because this does remain pretty heterogeneous -- is perhaps a slight increase in the pale green here, this proportion of viruses that have changes at 121 and that 135 K change that's increased over the period we've been looking at.

So before we talk about antigenic characterization of H3N2 viruses, I need to remind you that

this is difficult still because the viruses, the 3C.2a viruses that are cell-propagated, many of them have low or undetectable hemagglutination activity with red blood cells in the presence of oseltamivir, and we have to use oseltamivir in our HI assays now to control for changes in the neuraminidase upon cell culture that can confer some binding of the neuraminidase to the red blood cells. So we want to remove any possibility of looking at neuraminidase involvement, and that's why we add oseltamivir.

So only about 50 percent or less of viruses can be characterized by the HI assays. At CDC, we're at the higher end of this, we can now test about 50 percent of our viruses by HI, and that's up from about 25 to 30 percent in the previous year. But in addition, all of the WHO collaborating centers are doing one or other sort of virus neutralization assay, typically what we call either a plaque or focus-reduction assay, or a micro-neutralization assay. And these data are supplementing the data that we can obtain by HI.

So again this is an HI tree, an HI table. If you'll focus just on the numbers highlighted in yellow, again, these are antisera now raised to reference viruses grown in cell culture that are Hong Kong/4801-like. In many cases, and this is an example of CDC data, we can't actually use the Hong Kong/4801 virus itself. It doesn't

have sufficient HA activity in HI assays. But we can use these two reference viruses, Michigan/15 is our reference virus, and you can see here if we use the homologous titer of this virus, we can see that the circulating test viruses are all well inhibited by either this antisera or another antisera raised to another Hong Kong/4801-like virus, Hong Kong/7127.

If we look at the egg-propagated Hong Kong/4801 virus and antisera raised to it, you can see in this table we generally have the viruses, circulating viruses, are still well inhibited, they're having titers that are within fourfold of this homologous titer of 1280, but there are more examples where we see bigger differences, and you'll see even more of this in the neutralization tables.

We also have antisera raised to two 3C.2a1 viruses. One is a cell-propagated virus, Amman, and you can see again that antisera raised to this virus covers the circulating viruses quite well. However, an antisera raised to an egg-propagated 3C.2a virus, Alaska/232, doesn't cover the circulating viruses nearly as well, and in fact covers the viruses less well than the Hong Kong/4801 antisera raised to the egg-propagated virus.

We also have over here, I should have mentioned earlier, we're breaking these viruses down by their genetic clade, or subclade, and over on the far right we have key

substitutions that I've mentioned earlier. So we're really tracking the antigenic profiles of all of these genetic subgroups that are popping up. And the bottom line, by HI, you'll see some viruses here in the 2a's, the two different groups I mentioned, and in the 3C.2a1's, the different genetic groups I've mentioned there, and you can see that these viruses are well covered by antisera raised to the Hong Kong/4801-like viruses.

This is a neutralization test, a plaque-reduction assay, showing similar data. This is from our colleagues at the London collaborating center, and here, too, they have to use a surrogate Hong Kong/4801-like virus propagated in cells. That's shown in the highlighted red here. It's the Hong Kong/7295/2014 virus, and you can see antisera raised to this virus recognizes well the majority of circulating viruses tested. Again, these are viruses that were selected for the test because they have the different genetic changes that we're monitoring.

Antisera to the Hong Kong/4801 egg-propagated virus covers the viruses less well, as we saw in HI. And in neutralization tests this is more exacerbated in some labs more than others, because of the particular properties of the ferret antisera.

This is just the final antigenic test for H3N2. This is a focus reduction neutralization test from the CDC,

and you can see again that sera raised to either the cell-propagated Michigan/15 or Hong Kong/4801 that we can use in this test, in neutralization tests, covers the circulating viruses very well. And again, it's the different virus 3C.2a1 and 3C.2a viruses tested, represent the gamut of different genetic changes that we're seeing.

So, overall, we're not seeing a lot of antigenic change between 3C.2a and the 3C.2a1 viruses, and that's highlighted in the antigenic cartography. The 2a's are in the brighter red, I'm not sure how well you can see it, the 3C.2a1's are in the darker red, and we're seeing that they're clustering. The Hong Kong/4801 egg virus is on the edge of that cluster, and you can see now that the cluster is becoming more distinguishable from the earlier 3C.3a viruses represented by Switzerland, which was our former vaccine candidate in previous years.

But you can see that there's really overlap between the 3C.2a and the 2a1 viruses. And this is HI data. And the same is true of the neutralization data, it's just the data is a little more spread out because of there's just a little more heterogeneity in the titers of different neutralization assays.

So if we look at antisera raised to cell-propagated -- and now we're looking at how well all of the circulating viruses tested by all of the different

laboratories -- how well antisera to a Hong Kong/4801-like virus cover these, we can see that overall we get about 93 percent of the viruses can be characterized as Hong Kong/4801-like, with a smaller proportion, 7 percent, that are, we would say, show a greater reduction of eightfold or greater, and we would characterize as antigenically distinguishable.

If we use the antisera raised to the egg-propagated Hong Kong/4801, we don't get as good coverage, as I mentioned earlier, and it's around 60 percent now cover the viruses and 40 percent are not covered by this antisera. And if we look at data by the virus neutralization assays, we see that these numbers fall a little, but overall, again, the viruses tested by the different labs, most are well covered by the antisera raised to Hong Kong/4801, and we actually see, because of the problems with using Hong Kong/4801 egg-propagated virus and its antisera, in many of the virus neutralization assays, we get extremely high homologous titers, and even though the titers to the circulating viruses which are all propagated in cells, they still have robust titers. It just is, compared with that very high bar of a homologous titer, they all fall or predominantly fall into the low, that they're not being well covered by that antisera.

If we look now at -- this is an example again of the three panels of pre- and post-vaccination adult sera, this is again CDC data using the microneutralization test -- and here we're comparing, this is the vaccine virus, Hong Kong/4801, we're comparing the response to that cell-propagated virus. It's set here at 100 percent.

The numbers above here are the actual geometric mean titers of the different panels that we looked at. And you can see -- it's probably hard to see -- but we have a dotted line here set at 50 percent, and we're considering reductions if we're seeing significant drops below that red dotted line. And you can see for all the cell-propagated 3C.2a1 viruses that were tested, a number of them here, and an additional contemporary 3C.2a virus, that all of these viruses, the antibodies raised to Hong Kong/4801 vaccine virus, are reacting very well, similarly if not better than to the vaccine virus reference virus itself.

If we look at egg-propagated viruses, and this is one of the problems we have with egg-propagated viruses, we get extremely high titers, and this is also reflected in our human serology data. But overall, these egg-propagated viruses, if we compared them with egg-propagated Hong Kong/4801, we would also not see any drops in titer. So overall, we're seeing that the circulating 3C.2a1 and 2a viruses are -- that antibody raised to the vaccine virus

Hong Kong/4801 is still reacting well in human sera against these more contemporary circulating viruses.

And this is just another example of that. These are two additional human serum panels that some of the labs used. A China, we had pediatric, adult, and elderly, and Australian adult and elderly, and what's relevant here again is that they contained the Hong Kong/4801-like vaccine virus, and so this is data from Australia looking at adults vaccinated with the 16/17 QIV or TIV, or their Australian season, past season, 2016 vaccine. And again if you look at the dotted line of 50 percent response, and we look at the response -- this is HI data now, and they've used the Michigan/15 as their Hong Kong/4801-like virus -- you can see that's set at 100 percent, and a contemporary 3C.2a and a 3C.3a virus, are all very well covered by the antibodies that is raised against the Hong Kong/4801 vaccine component.

So in summary for H3N2, we did see a high level of activity in many regions of the world, and the majority of viruses fell into phylogenetic clades 3C.2a and subclade 3C.2a1. Ferret antisera raised against the cell-propagated 3C.2a viruses, for example the Hong Kong/4801-like viruses, well inhibited a majority of viruses tested, either in the HI or the virus neutralization assays.

And these included viruses within both the clade 2a and the subclade 3C.2a1, and also included a lot of those different little clusters that have formed and included are fairly diverse, genetically diverse, groups of viruses.

We saw less well coverage with antisera raised to the egg-propagated viruses, and as you know, egg propagation introduces additional changes that may affect antigenicity. And it's particularly problematic for recent H3N2 viruses. And overall the sera obtained from post-influenza vaccination human serology panels recognized the more contemporary 3C.2a and 3C.2a1 viruses well, regardless of the serologic test we used.

I'll move on to influenza B viruses. Again, not too much activity, some local activity in different parts of the world, in central South America, with some sporadic regional or widespread activity in just a few locations in Africa.

This is data from the WHO. They collected information, a total of over 15,000 B viruses, but a much smaller proportion, only about a little more than 20 percent, was actually had the lineage determined. But where the lineage was determined there was slightly more B/Victoria viruses at 58 percent, compared with B/Yamagata at 42 percent, so that's the overall global picture.

If we look and break it down by month now, and these again are these pie charts. The orange reflects the B/Victoria, the clade V1A. The blue, dark blue, reflects the B/Yamagata lineage, the Y3 clade that is circulating. And you can see by region that there was both circulating, that it really depended on the region as to which lineage predominated. In North America, as Lisa Grohskopf mentioned earlier, there's been a later uptick in influenza/B, and at the present time the B/Yamagata is slightly pushing out the B/Vics, but overall in North America it's close to 50/50 as it is in Europe. The Oceania, at the end of the southern hemisphere season, had a surge of the Yamagata, whereas in other regions like central South America, Asia, and Africa, they're still almost three-quarters predominating B/Victoria. So a very diverse picture.

And down below you can see this is all the data tracking over time and you can see it just changes month by month, and there's just this constant cycle of one lineage being a little ahead of the other.

Focusing first on the B/Victoria lineage viruses, again this is all of the data that was available to us. Each little line represents a sequence coming from a virus in the color-coded regions. The activity that we did have from September to January is all the V1A lineage, and

again, not too much diversity happening in the B/Victoria hemagglutinin gene. All of the V1A viruses have changes at 129 and 117, and apart from that, there's just a few sporadic things.

One thing that we did see in the United States, and we've only seen -- so the viruses that we've seen since September are, we've only seen a few of these viruses in the United States -- and there's a small cluster here that have a deletion of two amino acids at the tip of the molecule. And this is in an antigenic site, and this does have an antigenic impact, as I'll mention in a moment. But the other collaborating centers are searching for these viruses, they haven't seen them yet.

Again in the neuraminidase gene, not a lot going on there, or V1A. These are older viruses, but just to remind you that we occasionally see reassortants between the lineages, and these are some older viruses from 2016 or so, that have the Yamagata hemagglutinin and B/Victoria neuraminidase.

So if we look at an HI table for the B/Victoria viruses, again highlighted in yellow is the Brisbane/60 virus, either grown in eggs or grown in cells. Across the top are the antisera that we've used, and we're comparing the circulating test viruses, and these are viruses, a lot of them from the United States, but some from Europe, Asia,

and Africa, and they're all the V1A clade, and you can see that the majority of these viruses are antigenically well matched with antisera to the either egg-propagated or cell-propagated Brisbane/60. We do see some more fourfold reductions with antisera raised to the egg-propagated, but they're still considered Brisbane egg-like.

The exception are these viruses highlighted in blue, and these are the ones that have the deletion. You can see that this small group of viruses is antigenically distinguishable from the B/Brisbane, but as I said these are a small handful of viruses that we're seeing in the United States, and at this time what we're doing now is we're preparing antisera to these viruses to see if looking with that antisera whether we'll see antigenic differences or not, but we don't have that data available yet. These are very recent viruses.

And this is just to also demonstrate that the Texas/2/2013 antisera raised to cell-propagated Texas/2 virus also covers those circulating viruses very well, but again the viruses that have this deletion are not well covered by this antisera, indicating that they're likely antigenically distinguishable from either Brisbane or Texas viruses.

If we look at the antigenic cartography, it's telling us a story similar to what we saw previously. The

B/Brisbane/60 vaccine virus is shown here in red, this is the cell-propagated, and you can see that the 2016-2017 viruses shown in yellow are clustering tightly around it. The egg-propagated is a little more distant and that's because some groups, their antisera raised to egg-propagated Brisbane is a little more variable and doesn't cover these viruses as well.

The U.S. data -- so this is a summary of that data now, for all of the collaborating centers -- and you can see with our CDC data, we still get very good coverage with our antisera raised to egg-propagated Brisbane, similar to what we see with cell-propagated. Whereas some of the other collaborating centers have antisera that doesn't recognize circulating viruses as well if they've got the sera raised to egg-propagated. But everyone is seeing a high level of similarity if we're comparing with antisera raised to cell-propagated Brisbane.

This is again the true measure of whether we're seeing antigenic similarity or difference. And the differences we see here with egg are changes that we know occur with egg adaptation.

If we look at panels of human sera, and these are similar panels that I've already described so I won't go over them again, but this is now a compilation data from multiple laboratories that tested -- what we're comparing

here is the cell-propagated B/Brisbane reference virus and the antibody response elicited by the 2016-2017 vaccine containing the B/Brisbane component, and you can see with a few exceptions that these viruses are well covered.

This is a deletion mutant, so this is a sort of a rare virus, as is the Yokohama, and these are not covered as well. If we look at all viruses, some of them are not as well covered. But this example is again well covered.

We move on to B/Yamagata. So again, virtually all of the viruses detected in this period were of the Y3 lineage, and you can see some activity here in the recent months. If we look at a smaller tree we can see that viruses in pink and orange from recent months are all falling in the Y3 clade, and there's again not a lot of genetic diversity. There's some changes that are going on at residue 212 in a small group of viruses, or residue 252 in another small group.

Again, here we are seeing occasionally some reassortant viruses. And just to remind you, the reference virus, the vaccine virus here is the B/Phuket/3073/2013 virus.

Again, this is the neuraminidase. The vaccine virus is squarely in the center of the tree. There are some genetic changes here, but not ones that we're really

tracking to make changes for strain selection. And there's the rare Y2 virus there.

So if we look at the hemagglutination inhibition assay, this is a representative of data obtained from CDC, and shown in the highlighted yellow are the antisera raised to the B/Phuket/3073 vaccine virus, either egg-propagated or cell-propagated, and you can see again that the circulating test viruses from the United States and central South America, and one virus here from Oceania, are all well covered by the Phuket/3073 antisera, suggesting that these viruses are Y3 viruses, are still antigenically similar to the vaccine virus.

We also see that here, when we break down all the data from all the different collaborating centers, again, if we compare with antisera raised to egg-propagated Phuket, over 93 percent of the viruses are antigenically similar, 7 percent are low. And we see the same result if we look at antisera raised to cell-propagated Phuket. Again, overall, 93 percent of the viruses tested are characterized as being Phuket-like.

And again just showing this in a different way, here's an antigenic cartography visual, using HI data. You can see the B/Phuket/3073 egg-propagated vaccine virus shown in red, and the cluster of 2016 and 2017 viruses circulating. Some of these viruses that are a little more

distant reflect some of the greater differences that were seen in a minority of viruses for some collaborating centers.

If we again look at human post-vaccination sera from individuals that received the 2016-2017 northern hemisphere vaccine, this is again compared with the reference virus cell-propagated Phuket, set here at a 100 percent, you can see that the different circulating viruses tested were all well -- the antibody raised to B/Phuket covered well and reacted well with these different circulating viruses. So the B/Phuket vaccine virus is still reacting very well with circulating B/Yamagata viruses.

So summarizing, the influenza B viruses, B/Victoria, B/Yamagata lineage viruses, co-circulated at similar levels in some regions while in other regions the B/Victoria predominated in many countries.

B/Victoria lineage viruses all belong to clade 1A, it's the same clade we've seen for a number of seasons now, and recently circulating viruses are well inhibited by either ferret antisera raised to the cell culture-propagated Brisbane/60/2008 or the Texas/2/2013.

When we looked at human post-vaccination sera, we saw that there were some reductions compared to Brisbane, but this wasn't universally seen. The B/Yamagata lineage

viruses -- almost all of the viruses belong to clade 3, and the recently circulating viruses were well inhibited by antisera raised to either cell- or egg-propagated Phuket. And for the human post-vaccination data, again, the B/Phuket vaccine virus raised antibody that reacted well with circulating B/Yamagata lineage viruses.

So that brings me to the recommendation, which you've already seen earlier, but last week on Thursday WHO announced that recommendations for the 2017-2018 northern hemisphere influenza vaccine composition, and that was an A/Michigan/45/2015 (H1N1)pdm09-like virus, a Hong Kong/4801/2014 (H3N2)-like virus, and for the trivalent vaccine, a Brisbane/60/2008-like virus. For the quadrivalent vaccine, the second B component was recommended to be the B/Phuket/3073/2013-like virus.

And just before I finish, I just wanted to mention some of the new features that we're introducing in our vaccine virus selection. Clearly, as I presented last season, or the October VRBPAC meeting, we're recognizing that additional human serologic studies, particularly evaluating different birth cohorts, can make a difference, and so we're working to have better panels that we can do this for, perhaps also to address some of the questions for H3N2 VE where we're seeing some age-associated effects.

The other thing that we're doing now for each vaccination consultation meeting is we're hearing a report from the global influenza vaccine effectiveness group. So last week Alicia Fry from the CDC presented the data on behalf of the GIVE Consortium, and we heard the interim 2016-2017 results for H3N2 and B, and Lisa Grohskopf just told you about the U.S. data, but there was similar data from other regions, Canada. We also had the final estimates from the southern hemisphere for their 2016 season.

The other thing that we're now incorporating is several modelers who are doing viral fitness forecasting. They're taking our genetic data, and we're in a process of also folding our antigenic data in, in an effort to try and predict what the next emerging variant may be. But these data are only as good as the data that we have available at the time, so that's constantly the struggle, and even the modelers are recognizing that it's pretty hard to predict what's going to happen this time next year.

And then also we heard from CBER, they had some neuraminidase antigenic characterization data. So more to come on that.

So I'd just like to acknowledge all of the collaborating centers for all the work I've presented as well as the National Influenza Centers without whom we

wouldn't have these viruses to begin with, our Cambridge partners for antigenic cartography, and our many U.S. partners, particularly our partners at DoD that provide critical genetic information. And of course our CDC colleagues in Atlanta.

Thank you.

DR. EL SAHLY: So the story with the influenza B has been around 50/50 for a few years now, and it seems to be continuing that way, give or take. And given that the vaccine, quadrivalent versus trivalent, is also around 50 to 60 percent, the choice of Victoria not changing over different seasons -- I'm thinking about what would be a benefit, or if it would be of a benefit, to include the Yamagata on subsequent seasons. You know what I mean? Like, alternate, or if the story is continuing to be 50/50, and our coverage of quadrivalent is still not moving fast enough --

DR. KATZ: It's not always 50/50. I would say that several seasons ago we had predominantly B/Yamagata. Last season in North America at least we saw an increase of B/Victoria, and that continued but didn't take over the B/Yamagatas. But in other regions of the world there has been more B/Victoria, and really the decision that the group made last week was -- and it was a tough decision -- but we really considered the countries and the regions

where B/Victoria was still predominating, and we heard that they were regions of the world that were more likely to have only trivalent inactivated vaccine. We know in -- it was probably around 60 percent usage in the United States this year. It may increase.

And in other regions like Australia they are moving totally over to quadrivalent. So when some of the more European, Australia, U.S. countries, there is this move to quadrivalent. So we felt that the decision for trivalent should be focused more in regions where they didn't have access to quadrivalent vaccine. That was one reason that we made that selection.

Also I think -- and we looked at past VE data, we looked at how the viruses have changed, as you say, from season to season, the epidemiology, and it was really very difficult to come up with a pattern that -- we can't predict if B/Victoria or B/Yamagata will be predominating next season, at least in North America or anywhere else. We expect both will be circulating.

DR. EL SAHLY: So, given that the bulk of individuals who receive -- everybody who got trivalent last year, we can predict that they may be partially protected against Victoria next year, partially. But we did not use trivalent Yamagata, and it seems to be 50/50 or 40/60 every year. You know what I'm getting at with this?

DR. KATZ: I think so, but I really think it's hard to pin what we're seeing epidemiologically with what's in the vaccine. We do know the B/Victoria this year, as we were seeing last season, that it's largely people under the age of 25 that are getting infected with B/Victoria.

DR. MONTO: I was going to say the good news is there's a lot more cross-protection between the lineages than we originally thought. When decisions were made to go over to quadrivalent vaccine, one wonders whether those decisions would have been the same if we had had some of our VE studies that we've had recently.

My question is about 3C.2a1. Because I have reviewed some papers from Europe which say that vaccine effectiveness has gone down since 3C.2a1 strains have come in. There's clearly cross -- in terms of antigenic cartography, they cluster together. Are some of these outliers, the ones that have lost glycosylation sites and the rest, are they responsible, or is this just early numbers in terms of some of the studies? Some of the studies from Europe have had really small numbers and almost ecologic conclusions about why they were seeing these drops.

DR. KATZ: Yeah, I would agree. We will do the subclade analysis when we have our final data. Obviously that's not helpful here. But for the Canadian studies they

did do a breakdown of VE against 3C.2a1, and it was similar. I think it was about 43 or 44 percent, which was what their overall H3N2 VE was, similar to what we saw in the United States.

I think some of the other studies that are coming out, and there are some studies from Europe that are naming new genetic groups, there's a group that are calling something 3C.2a2, and the WHO group hasn't really -- we recognize the group they're seeing, but it's a very local circulation of particular viruses, and I don't know that we can really ascribe too much to the VE that is being seen because of the small numbers when they break it down.

Certainly in our panels of post-vaccination human sera, we saw that antibody elicited by the 2a virus, Hong Kong/4801, reacted just fine with the 3C.2a1 viruses we tested in multiple labs.

DR. BENNINK: The 2a2 -- that was the one -- they had two clusters, but wasn't there one of these that had the glycosylation change?

DR. KATZ: Yes, it was within the 3C.2a group, and it had a change at 144. So it was one of the groups I highlighted.

DR. BENNINK: Which then, if that takes off, that's really going to be a major change.

But do you have any potential candidate vaccines, do you have anything like that, that in your antigenic cartography, centers more within what's circulating, whether they're 2a or 2a1, whatever it is, because the virus that we're using here, is kind of off to the side some. Do you have anything that's a potential candidate vaccine that's more centered?

DR. KATZ: So, a couple of candidate vaccine viruses are in development, for 3C.2a1. I did point out one that was developed here. CDC sent a virus, Alaska/232, for reassorting, and its antisera I showed you in an HI really poorly covered circulating viruses. So we really just don't think that's a good candidate. There's another candidate that is under development, but there's just not sufficient data to say whether it would be better or worse than the Hong Kong/4801 virus.

DR. BENNINK: That was the Alaska one? Or --

DR. KATZ: The one I mentioned. There is another European virus that several of the reassorting labs have at present, but it's months away probably from having a candidate.

PARTICIPANT: But the Brisbane is not very far? I think there was one, Brisbane?

DR. KATZ: For H3N2?

PARTICIPANT: Yeah, I thought so, but maybe I'm wrong. I thought you had a slide there. But the ones in Europe, is that Bolzano? Or is that Scotland? Or something else?

DR. KATZ: There's a Norway virus that has gone to several reassorting labs, and I think I -- in one of the neutralization tables they had antisera raised to the cell-propagated Norway virus, and it covered quite well. The question always is what's it going to do in eggs?

DR. GREENBERG: Perhaps you answered my question about the 3C.2a and 2a1, but I was curious as to why -- and I see the data -- but I was a little bit surprised that there isn't a better match with the 3C.2a1, because as was just said, that's the circulating strain. So I would have thought just intuitively, that a strain for vaccine that's a 3C.2a1 would be a better antigenic match to the 3C.2a1 circulating strain.

DR. KATZ: We're not seeing that in our antigenic data. We're really seeing the antisera to the Hong Kong/4801 covers these viruses just as well -- the 2a1's just as well as the 2a viruses.

DR. GREENBERG: And I have a follow-up question about the B lineages. I was struck that for North America, most recently, say January of 2017, you did show that there was an uptick of the Yamagata, and you know again, it'll be

a difficult decision for the committee. Does that -- should the committee consider that in deciding which should be in the trivalent and which should be in the quadrivalent?

DR. KATZ: I can only give you the example of the H3N2s last season, where we saw quite an uptick of 3C.3a's and we were really concerned that -- and that was at the end of the season, and we'd already made the selection of Hong Kong/4801, which is a 2a, and there was concern that maybe this season we'd see 3C.3a's, and they just went away. We saw a few of them, but not many, so it's really hard to predict.

DR. GREENBERG: Okay, thank you. Just one final question about the B. I noticed on the phylogenetic tree that the B/Brisbane is a bit far from the current circulating strains, but yet the antigenic and the ferret sera seem to work out.

DR. KATZ: There just haven't been that much genetic diversity in the Bs. They tend to evolve a little more slowly. And we haven't seen the impact on the antigenicity. We do continue to make new candidate vaccine viruses to that group, but we haven't found anything that's performing better than the Brisbane.

DR. MOORE: I was really struck by your data on the microneuts that you showed for the Hong Kong 3a strain,

the H3 strains. It's a yellow slide, and it shows cell versus egg, virus -- four different participating centers that did microneuts. And I always think that neuts are much better than hemagglutinin inhibition assays for actually telling us whether the vaccine will be effective in giving us sterilized immunity for infection. So perhaps it's a good thing that this virus doesn't have a very good HI activity.

But here what we're seeing, if I understand this correctly, is the egg-derived strain, which is the same way that most vaccines are made, is giving only coverage to about 19 percent, and so it's a complete disconnect from the cell-based, whereas you don't see that for any of the other, for the B virus, and the H1.

DR. KATZ: Right, and as I alluded to, but probably didn't explain specifically -- and we can use the CDC data as an example -- so we get very good concordance when we use antisera raised to cell, but our antisera raised to the egg-propagated Hong Kong/4801-like virus has an extremely high homologous titer, and unfortunately I don't have an example.

So this isn't an extremely high homologous titer, but this is data from the Crick London collaborating center. But you can see that there's more 40s and 80s with egg-propagated by neutralization. With our data we have a

titer that is -- for our antisera -- that is thousands, it's over 5,000. So even though we're getting reasonable titers, that difference is just so much greater that we have to call them, that they're low reactors.

So it's a property of the egg viruses, both how they perform, and an example of that is -- so in neutralization tests, this is human sera, but you can see we're getting extremely high titers whenever we use egg sera. So what we're doing in the HI or the neutralization we're taking sera raised to egg-propagated viruses, and sometimes these egg adaptations confer properties on the virus and the antisera that cause very high homologous titers. And we're always comparing to cell-grown viruses that always have a lot lower reactivity. So it's a struggle. But you're right, there is that problem.

DR. MOORE: So, does that help us? I guess what you're saying is, because egg titers have such a high titer neutralization, then your non-homologous neutralizations are going to be manifold lower, and are going to look lower, but they're still effective neutralizations, is what you would predict. However, we know the vaccine efficacy for this strain against virus that we're seeing is not that great, and it's likely to get worse.

DR. KATZ: It's not great. I think the best we can do right now is match the vaccine strain as close to

the circulating strain as possible, then the current year's data and past data suggest we'll be around 40 percent. Is that satisfactory? No, it's not. We need to do better for the H3N2s.

DR. MOORE: I guess my question then is, apparently there is new MDCK-derived vaccine that's been approved. Is that right? I'm not clued in to that.

DR. KATZ: So one company that is licensed in the United States, and FDA may want to jump in, produces the vaccines in a proprietary MDCK cell line, and last year FDA approved that the seed virus, the starting material, can also be grown in cells. Prior to that, even though the vaccine was manufactured on a cell platform, they still had to start with an egg-grown virus. And if you start with an egg-grown virus you've still got those egg adaptations.

Now FDA has agreed or approved the use of a cell-propagated seed virus. And so we hope that as these changes -- as recommendations are made -- that cell-based candidate vaccine viruses will be used in the future, and will overcome that egg issue. For that vaccine only.

DR. MOORE: So we don't actually have the neut titers here. We just have the differences in eightfold and not within each group. But I guess what I'm trying to get a feeling in my own mind is, is it likely that the cell-

grown virus will have better neutralization activity and hence better vaccine efficacy for the Hong Kong strain?

DR. KATZ: We can't say. And unfortunately, it's not a major proportion of the vaccine that's used, so as Lisa mentioned, it's very difficult to get vaccine type-specific information because of the variety of vaccines that are used in the United States. But my understanding is that that is still -- and maybe the manufacturers want to address that -- but I'm not sure what proportion of the U.S. market that would represent. But it's small.

Overall, the majority of flu vaccines are still egg-based, more than 90 percent. A small proportion of the market is the recombinant HA, which could again potentially overcome the egg issue and the cell-based product.

DR. EDWARDS: Thank you, Jackie. I think for now, time for a break. We're about 15 minutes late, but I think we can still have a 15-minute break, maybe 20 minutes.

(Break.)

Agenda Item: DoD Vaccine Effectiveness Report

DR. EDWARDS: The next report will be the DoD Vaccine Effectiveness Report given by Dr. Michael Cooper of the Respiratory Infection Surveillance Global Emerging Infection Section of the Armed Forces Surveillance Branch in Silver Springs. Dr. Cooper.

DR. COOPER: Thank you. This is my disclaimer. So, good morning. As is mentioned, my name is Michael Cooper, and I am the lead for Respiratory Infection Surveillance with GEIS, which is the Global Emerging Infection Surveillance section of the Armed Forces Health Surveillance Branch. We are a DoD asset. Today I will be presenting data from the 2016-2017 season midyear report from our Influenza Surveillance Network.

Included here will be surveillance data from our partners in North America, South America, Asia, Africa, and Europe, as well. In addition, surveillance data will also be presented on military recruits here in the United States. I will also be presenting a brief summary on phylogenetic analysis developed by our partners at the United States Air Force School of Aerospace Medicine, also referred to as USAFSAM.

In addition, I'll be presenting three midyear estimates of vaccine effectiveness developed by the Naval Health Research Center in sunny San Diego and USAFSAM in not-so-sunny Dayton, Ohio, and the Armed Forces Health Surveillance Branch right down the road in Silver Spring.

I just want to take a moment to give you a little background on my organization and our influenza surveillance network. Again, we are a DoD asset and we're dedicated to surveillance of infectious diseases primarily,

but not exclusively, in military populations. Our influenza surveillance program extends to over 30 countries and has over 400 sites in those countries.

In addition to monitoring United States military infectious disease, we have partners who have relationships with foreign governments, ministries of health, ministries of defense, which provide disease surveillance data on local and national populations. On average our network collects and analyzes about 30,000 influenza or respiratory samples per year and send between 300 and 400 sequences to GeneBank each year.

Here is a map of where we are in the world. You'll see the blue spots are countries where we have surveillance, either local national populations or military. You'll also see some red dots there. They are embassies that we also have in our network who can send samples to us whenever they need to.

The first graph I am going to share with you is on United States military recruits. These are individuals going through basic training. Basic training usually lasts anywhere from two months to thirteen weeks depending on the service. About 180,000 individuals go through basic training each year. It is a rigorous process. It's a very stressful, sleep-deprived process.

Along the X axis, you'll see are epi weeks. You'll see there are three years' worth of data there for comparison. Along the Y axis on the left-hand side, you'll see it is the number of specimens tested, and the Y axis on the right-hand side is the percent positive.

It's an interesting group to do surveillance on, especially for respiratory disease. Historically, up to 20 percent of a recruit class could be hospitalized for respiratory infections. They are very much at risk. They are also a highly-vaccinated population -- 100 percent vaccination for influenza, also 100 percent for various other viruses as well.

If you take a look here, you'll see this is adenovirus -- that's what I was searching for, sorry -- you'll see that we're color coordinated regarding our influenza subtypes, H3 being the green, H1 being the blue, and dark blue is influenza B. If you look at the far-right hand side, you'll see that this data goes out through February and it is primarily H3N2 season that the recruits are experiencing -- little bit of influenza B.

What's interesting to look at in addition is -- if you look in July and August timeframe, weeks 20 and 31, or 16 and 19 in May, you're seeing spikes in influenza and that's not terribly unusual in the recruit classes. This

highlights the need for year-round surveillance in this particular group.

These data are from North America. These are active duty military members and dependents. Also a select civilian population near the Mexico-California border. Again, relatively mild season, H3N2 by and large.

In Europe, we have about 190,000 individuals in Europe, about a third of that being active duty military, the rest being family members and dependents. And you can see, by and large, they are seeing H3N2 as well. The countries covered in this surveillance are our U.S. military members and family members stationed in Germany, United Kingdom, Turkey, Spain, Italy, Belgium, and Portugal.

Our data from Latin America comes from Peru, Paraguay, Columbia, Nicaragua, and Honduras. It is a mix of U.S. military members and local national populations. Of course, these countries fall within a tropic band, so you wouldn't expect a flu season, per se. Looking at the most recent data, you'll see influenza B and H3N2 represented.

These data come from our partners in Asia and countries represented here are Nepal, Philippines, Bhutan, Indonesia, Cambodia, Korea, Japan, and Thailand. You're probably aware that we have sizable military populations in

Japan and Korea, so this is a mix of local national populations and U.S. military. As you can see, the far-right hand corner, it's a mix of H3N2, Flu B, and some not subtyped. Again, these countries fall within a tropic zone, so you wouldn't expect a flu season at this point.

These data come from East Africa. It's Kenya, Uganda, and Tanzania. The most recent data for the past few months is a mix of H3 and H1 with some influenza B as well.

In summary regarding our circulating strains in surveillance, North America and Europe, military members and dependents have experienced low to moderate flu activity so far. Positive samples have been primarily H3N2. Globally, there is a mix of H3N2 and H1 with some influenza B as well.

Now I am going to present to you some phylogenetic analyses and to start off with, I think it's fair to say that the majority of these analyses were reported on; they're a subset of Dr. Katz's analysis with the exception of some of the more recent sequences obtained on H3N2. So I will probably go rather quickly through H1N1 and the Bs and concentrate a little bit more on H3N2 for the sake of time.

This graph here gives you some idea as to where in our network our sequences have come from. The map shows

-- well, for these analyses, 412 sequences were collected. 83 percent of those were influenza H3N2, 5 percent were influenza H1N1, and 10 percent were influenza B/Victoria, and 3 percent were influenza B/Yamagata. These sequences come from 16 countries over five continents. The H3N2 was the predominant subtype in all regions except for in Africa and East Asia, where B/Victoria was either equal to or greater than the number of sequences for H3N2. And that's just a summary of basically what I just told you.

So looking at H1N1, all 19 of the H1N1 sequences collected were in clade 6B; 79 percent of those were in subclade 6B.1. The component that is recommended is A/Michigan/45/2015-like virus. Looking at the H3N2 phylogenetic analysis, 150 of the 341 H3N2 sequences collected from 2016 through 2017 so far were selected to represent clade proportions as well as geographical and temporal distributions.

About 7 percent of the sequences were in clade 3C.3a, 65 percent were in 3C.2a1, and 11 percent were in the proposed clade, 3C.2a2, while 16 percent were in 3C.2a with no further subclade designation. The recommended component for the 2017-2018 vaccine is A/Hong Kong/4801/2014-like virus.

I won't spend a lot of time on this graph, it's just there to demonstrate the genetic dynamic nature of

H3N2. You'll see that this is from July to January looking at amino acid substitution. You'll see in the top two, N171K and N121K, lots of substitutions. Go down to 158V, little to none. So again, this is just designed to highlight the dynamic nature of H3N2, as Dr. Katz already has.

Looking at influenza B/Victoria, all 39 of the influenza B/Victoria sequences were from clade 1A. Three strains were found to have a deletion at amino acid positions 162 and 163. The recommended component for the 2017-2018 vaccine is either B/Texas/02/2013-like virus or B/Brisbane/60/2008-like virus.

Finally, looking at B/Yamagata, all 13 of the influenza B/Yamagata specimens were in clade 3. The recommended component of the quadrivalent vaccine is B/Phuket/3073/2013-like virus. There is a summary in your handouts, so you can refer to those.

As I mentioned, I'm going to present information on three vaccine effectiveness studies. As I've mentioned, to this point, the flu season has been relatively mild in most regions covered by the DoD influenza network. In some instances, there is not enough cases for detailed sub-analyses. The analyses have been somewhat simplified, due to the fact that LAIV is not being used and the fact that there is too little H1N1 in some cases -- well, actually,

in all cases -- to look specifically at the vaccination effect for H1N1 specifically.

So these midyear estimates are provided by the United States Air Force School of Aerospace Medicine, Naval Health Research Center, and Armed Forces Health Surveillance Epi and Analysis section. Each uses the case-control method. Each uses logistic regression to estimate the vaccine effectiveness, or to estimate the odds ratio, which is then used to calculate the vaccine effectiveness. Two studies used control-test negative method, and the study conducted by the Epi and Analysis group at the Armed Forces Health Surveillance Branch used Health Controls rather than test negative controls.

No analyses by H1N1, I should say. Again, it was an H3 dominant season. Each influenza infection was confirmed by PCR or viral culture. And here is our testing criteria, which is a little bit different from CDC's. We still use fever of 100.5 as one of the criteria. Cough and sore throat, and the specimens should be collected within 72 hours of the onset of symptoms.

These analyses look specifically at healthcare beneficiaries, not active duty members. So it is the children and spouses of military members. The time period is from October 12, 2016 through February 18. The analysis was by influenza subtype, H3N2 and B, and by age group,

children versus adults -- those under 18 versus those above 18. Adjusted for age, month, and illness. Statistically, we had 534 cases, that comes down to about 477 after missing data are accounted for. These cases again were confirmed by PCR or viral culture, and we were able to come up with 838 test negative controls. This is far from optimal. This is about 1.5, 1.6 controls to cases. Usually, you'd like 4:1.

Vaccination rates, about 32 percent of cases were vaccinated, and 36 percent of controls were vaccinated. 89 percent of the cases were H3N2, 1 percent was H1N1, and 10 percent influenza B. Here is your age breakdown. Again, 60 percent of our cases were under the age of 18. About 40 percent were over. And a slightly finer look at the age distribution, and you can see that about 18 percent were over the age of 50.

So the adjusted estimate for vaccine effectiveness. H3N2 overall adjusted VE was moderately protective and statistically significant for influenza H3N2. VE was 42 percent. This was statistically significant for children, not so for adults. Again, 60 percent of our cases were under the age of 18.

For flu B, the overall adjusted VE was moderately protective and statistically significant for influenza B, a VE of 53 percent. When looking at this, it was looking at

all flu Bs, but about 77 percent of those with influenza B were under the age of 18. So the vast majority were children.

Here are your adjusted estimates of vaccine effectiveness, confidence intervals, and your VE estimates. You can see that the all dependents, vaccinated versus unvaccinated, 42 percent vaccine effectiveness, with a confidence interval of 24 to 56. Looking at adults, just the individuals above the age 18, or 18 or over, you have a VE of 32 percent. It's not statistically significant. And looking at individuals under 18, you have a vaccine effectiveness of 48 percent. Looking at all influenza Bs, you have a vaccine effectiveness of 53 percent. That is statistically significant.

The next estimate of vaccine effectiveness I'm going to share with you, the population used in this study was DoD dependents in Southern California, Arizona, and Illinois outpatient clinics and civilians near the U.S.-Mexico border, specifically the California-Mexico border.

These analyses are adjusted for study populations, military dependents versus Mexico border civilians. Only obtained 75 cases, which is the lowest I've seen since I've been involved with this work, and that's several years. It's usually in the neighborhood of 150 or so, or 130, so not much in the way of sub-analysis.

We weren't able to do many sub-analyses with such a small number of cases. Each of those cases was confirmed by RTC-PCR.

Selected 224 test negative controls for a 3:1 ratio. The vaccination rates for cases was 33 percent, controls 48 percent. 93 percent of the cases were H3, 4 percent were flu B, and 3 percent H1N1. Almost, well, 68 percent, almost 70 percent of the cases, were under the age of 18, and about 30 percent of the cases were between the ages of 18 and 64, with no one above the age of 65.

So the VE for H3 was moderately protective and statistically significant. When parsing it out by age group, for children, the VE was -- the point estimate was moderately protective but it was not statistically significant. And here is the odds ratios and the VE internals for that analysis, about 46 effectiveness for all. Again, we're running into statistical power issues here.

Now this analysis is for active duty members only. And rather than using the test negative controls, we use health controls, and again these are Army, Air Force, Navy, Marines, and Coast Guard members, both located within the United States and outside of the United States. There were 987 lab-confirmed cases, and these are confirmed by rapid test, PCR, or culture.

There were 3,709 health controls selected. These were individuals with medical encounters for injuries or mental health conditions, with no ILI reported at the encounter, and no medical encounters for influenza during this flu season. And they were matched to cases by sex, age, date of encounter, and location.

The models also adjusted for a five-year vaccination status. And that's a dichotomous outcome, yes or no? So we'll probably talk about that a little bit more later.

Obviously we're dealing with a truncated age distribution here. You're not going to see people under the age of 17 certainly, and you're probably not going to see many people above the age of 60 in the active duty population. And so here's the distribution: 91 percent of cases were vaccinated; 89 percent of controls were vaccinated. You can see there's going to be problems in trying to calculate an odds ratio here. It's really difficult to find a vaccinated case, or an unvaccinated case I should say, under these circumstances.

Six hundred and thirty-six of the influenza As were unsubtyped. They tend to come from clinical areas that don't do subtyping, 261 of the H3N2s, or I should say, influenza H3N2, there were 261 cases. And only 12 H1N1s, and 79 influenza Bs. Ninety-three percent of the cases and

95 percent of the controls had prior vaccine in the previous five years.

And obviously we're very well matched, cases to controls. The majority of your cases, about 37 percent, are between 30 and 39. And 18 to 24, there's about 30 percent of your cases are between 18 and 34.

Estimates for influenza A, the VE estimates are very low, and not statistically significant. We have wide confidence intervals, low power due to relatively small numbers and very high vaccination rates. For flu B numbers were too small to produce reliable estimates, so we don't include any in this presentation.

And here are your vaccination estimates. VE estimates, as I should say: 3 percent for influenza A, 33 percent for influenza H3N2.

And this is a summary of everything I've presented here. Again, for dependents and civilians overall the VE for H3N1 was moderately protective and statistically significant. VE against flu B was moderately protective and statistically significant in the USAFSAM analysis. For active duty military members, VE was not statistically significant for influenza A. So, our limitations.

Obviously, these individuals were sick enough to seek medical attention. So we can't really comment on

vaccine impact for less severe cases. Active duty military members are highly immunized. This could have a negative impact on VE, potential methodological issues, power, and potential biological effects such as an attenuated immune response with repeated exposures.

The populations in this work are younger, so we can't really comment on vaccine impact in older, high-risk populations. USAFSAM analysis was limited by a suboptimal control-case ratio, but yet they found statistical significance for H3N1 and for B. So the effect size must be rather robust.

The NHRC analysis, we're limited by very small numbers. Only 75 cases. And the Armed Forces Health Surveillance Branch analyses were limited by high vaccination rates, low statistical power, and other potential issues.

I'd like to thank our partners from basically throughout the world. And I'm happy to take any questions.

DR. EDWARDS: Questions?

DR. MONTO: The first VE analysis, there was a rather a large difference between the unadjusted and the adjusted rates, unlike the next one, which looks more like what we usually see. Is there any explanation for why the crude and the adjusted were so different?

DR. COOPER: I could only offer a guess, and that's I would imagine it has to do with the differences in the proportion to gender. These are, again, dependents. These are not active duty members.

DR. MONTO: The next group was pretty close. Again with the same point estimates. Very curious.

DR. COOPER: Very different populations, case sizes as well, and the fact that -- this one here, this is the second one you're talking about?

DR. MONTO: Yeah. This is more like what we're used to seeing.

DR. COOPER: Well, it could have to do with unanalyzed confounders, or some interaction that's been untested.

DR. JANES: Related to that point, I was going to ask who the controls were for these first two studies. You know, how comparable are the cases and controls, and big differences between the groups could explain --

DR. COOPER: For the first study, the controls are also military dependents, spouses and children. For the second they are all -- for the NHRC study they are all again, military members, and individuals who use a clinic, a number of clinics on the California border. So they're all selected from the same populations. And in addition, which the NHRC analysis, they do what they could

statistically to try and control for whether they were military or border, by putting that in the model.

DR. EDWARDS: I thought your inter-influenza season data were interesting. So you do see a lot of clustering of influenza in non-influenza seasons in the recruits. Could you talk a little bit about that? What strains are they, do they come from southern hemisphere, or sort of what are your thoughts about that?

DR. COOPER: Well, if we go back to the original, what we saw last summer was H3N2. That's not always the case though. In this particular case, it's not unusual to see little spikes, and sometimes large spikes, of respiratory infection during the summer months. You have people coming from all over the country, with varying immune profiles, varying experiences with viral infections, being put together in close confines under a lot of stress. So many, all sorts of things become problematic. Generally speaking we don't see a lot of adenovirus in the civilian population. But you see plenty of adenovirus -- before we had the vaccine back, it came back in 2011 -- you were seeing very large numbers of adenovirus and high numbers of hospitalizations as well. So it's a very unique kind of population.

DR. EDWARDS: The next discussion will be on candidate vaccine strains and potency reagents, by Dr.

Joshi, lead biologist at the Divisions of Biologic Standards and Quality, Office of Compliance and Biologics Quality at CBER, FDA. Dr. Joshi?

Agenda Item: Candidate Vaccine Strains and Potency Reagents

DR. JOSHI: Good morning, everybody. I am Manju Joshi, and I work in the Division of Biological Standards and Quality Control in the Office of Compliance and Biological Quality at CBER. The Division of Biological Standards and Quality Control -- we call it DBSQC to short, it's too long a name -- in collaboration with other essential regulatory laboratories, participates in generation and calibration of reagents required for testing of influenza vaccine.

Our division also manages and provides these reagents for all the U.S. licensed manufacturers. In this presentation I will give you an update on the candidate vaccine strains and go over our division's goals towards preparing and supplying influenza vaccine testing reagents for the 2017-2018 season.

In my presentation I will go over currently used vaccine strains and WHO recommendations for 2017-2018 seasonal vaccines, both trivalent and quadrivalent. I will also update you on the status of available reagents for each of these strains, and I'll make some general comments

which will be not so much for committee, it will be for the other members in the audience, especially the industry representatives.

Coming to the influenza A of H1N1 type. For H1N1 type, the current vaccine strains was A/California/07/2009-like virus. A number of reassortants have been used in the manufacture of vaccine last season. This included X-179A and X-181 reassortant for A/California/7/2009 and NIB-74 and NIB-74xp for A/Christchurch.

And I'm sorry, I'm just not going to say all the numbers because they're too long, so we'll just restrict ourselves to a short name.

And at the same time, A/Brisbane/10 and another A/California-like virus was also used in vaccine manufacturing. Last season CBER provided reagents for egg-derived A/California X-179A and X-181 reassortant. Similarly NIBSC UK had provided reagents for NIB-74 reassortants as well as A/Brisbane/2010 wild type cell-derived virus.

The WHO has recommended the strains for 2017-18 and I think by now each speaker has gone over it, and we know that the recommendations comes as A/Michigan/45/2015 (H1N1)pdm09-like virus. Given here is the list of candidate vaccine viruses that has been recommended for this group. And as all of you know in this audience, that

this strain also been recommended for 2017 southern hemisphere season.

Coming to the status of the reagents. This is provided. We all understand that inclusion of WHO proposed strains in the vaccine is based on the approval by the committee today. If this strain gets approved, we'll just take a look at where we stand in terms of the reagents.

Let me point out that CBER is in the process of getting reagent ready for A/Michigan/45/2015 X-275 reassortant. The antiserum preparation is ongoing, and as soon as antiserum is ready, the calibration of reference antigen will be initiated.

Since this strain was recommended for southern hemisphere campaign, NIBSC had prepared reagents for A/Michigan/45 X-275, while for A/Singapore/GP1908 IVR-180, reagents were prepared by both TG Australia and NIBSC UK.

TGA worked and have already prepared a cell-derived reagent for A/Singapore/GP1908. Please note, again this is more for the audience part, please note that CBER will authorize use of reagents from other ERLs if this strain is selected today, and this will be on a case-by-case basis, and we really request the industry participants, representative, to get the feel that we would like you to consult with DBSQC prior to using any reagents from other ERLs.

Coming to the H3N2 strain, for 2016-2017 season, A/Hong Kong/4801/2014-like virus was recommended. A/Hong Kong/4801 and its reassortant X-263 were used for vaccine manufacturing. SRID reagents for the potency-testing reagents for egg-derived X-263B reassortants were made available by CBER as well by NIBSC. Reagents for cell-based A/Hong Kong strain were prepared by CBER and provided.

This year, as all of you know, that WHO has recommended there be no change in this strain for 2017-2018 season, and a number of candidate vaccine viruses, both the egg-derived and cell-derived, have been proposed. I'm not going to read any of these names in the interest of time, and we all know that the same strain has also been recommended as an H3N2 strain for 2017 southern hemisphere season.

If this strain is selected by the committee today, here is the status of the reagents. For A/Hong Kong X-263B reassortant, which was used last year in vaccine manufacturing as well, CBER had prepared reagents and those reagents are still available. Similarly reagents for the same 263B strains are also available from NIBSC and TGA.

Reagents for reassortant X-263 were prepared were prepared by NIAID last year and they are available. In addition, reagents for A/New Caledonia/71 reassortant were

prepared by TGA last year and they are still available. Last year CBER had prepared reference reagents for cell-derived A/Hong Kong, and we still have those reagents available. As far as antiserum lot, we usually get depleted over a period of time faster than anything. Currently we have two lots of antiserum available for vaccine testing, and preparation of additional antiserum lots for testing are planned in coming months.

And again, I don't have to say again, the blue words say, please consult.

Coming to the influenza B virus from Victoria lineage. For 2016-2017 northern hemisphere season, WHO had recommended that the B strain for trivalent quadrivalent vaccine B be B/Brisbane/60/2008-like virus from Victoria lineage. Last year, wildtype B/Brisbane/60 and B/Hong Kong/259/2010 viruses were used in vaccine preparation. A number of reagents were made available for different B/Brisbane/60-like candidate vaccine viruses.

For testing of egg-derived product prepared using B/Brisbane/60 reagents were provided by CBER, NIBSC, and TGA, and predominantly CBER reagents were used in testing. Similarly reagents for cell-derived B/Hong Kong were provided by CBER. Again, no change has been recommended by WHO for this B strain for either trivalent or quadrivalent

vaccine, and, again, their recommendation is to continue B/Brisbane/60-like virus as the B component in the vaccine.

Again, I'm not going to read all, but there are a number of egg-derived candidate vaccine viruses, they are both wildtype as well as the reassortants which have been prepared, as well as cell-culture derived viruses of this group are available. Again, this recommendation was made even for the southern hemisphere 2017 campaign.

If today committee selects this strain, let's go over the status for the reagents we have available for vaccine testing. So, egg-derived antigen for B/Brisbane/60 is available from CBER. Egg-derived reagents for B/Brisbane/60 is also available from NIBSC and TGA. Reagents for the reassortant BX-35 are available from NIBSC as well. Again TGA has reagent available for another B/Brisbane/60-like virus which is B/Brisbane/46, and NIAID Japan has reagent for B/Texas/2/2013 virus.

CBER had last year prepared cell-derived reagent for B/Hong Kong/259 and that is available. CBER also has reagents for B/Brisbane cell-derived and NIBSC has prepared a reagent for reassortant BX-35 cell-derived. As far as CBER's status of the antiserum is concerned, we have a lot of antiserum available in our stock, and we are in process of preparing additional lot of antiserum. And this is all in plans.

Again, the blue words are there to remember.

Coming to the influenza B for quadrivalent formulation. As we all know, quadrivalent vaccines are supposed to contain three strains that are recommended for trivalent vaccine, with an additional B strain from alternate B lineage, referred to as the second B strain. For the 2016-2017 northern hemisphere season, WHO had recommended that quadrivalent vaccine contain B/Phuket/3073/2013-like virus from Yamagata lineage. Last year wildtype B/Phuket and wildtype B/Utah, which is also a B/Phuket-like virus, were used in vaccine production.

For egg-based product prepared using B/Phuket virus, reagents were prepared by CBER, NIBSC, and TGA. For cell-based product prepared using B/Utah strain, CBER and NIBSC had prepared reagents. As we all know, for 2017-2018 WHO recommendation is that there be no change for the second B strain for quadrivalent vaccine.

I'm not going to go over again the list of the various candidate vaccine viruses, which are available for both the egg-derived ones and cell culture-derived. Again, this is the same strain which has been recommended for 2017 southern hemisphere season. Looking over the current status and availability of the reagents, we have the reagent at CBER available for wildtype B/Phuket. Reagents for wildtype Phuket are also available from NIBSC, TGA, and

NIAID. Reagents for egg-derived B/Brisbane/9 are also available from NIBSC. For cell-derived product, reagents for wildtype B/Utah strain were prepared by CBER and they are available. Similar reagents were prepared by NIBSC and they are also available.

Currently CBER has three different lots of antiserum available, so we are good on that.

So now, coming to some general comments. This is mostly directed for the users of these reagents. Please remember that only CBER-authorized reagents should be used to test potency of vaccines marketed in the United States, and we really request please consult with CBER before starting to use any reagents. And as all of you know, CBER collaborates with other ERLs in calibration of reagents, and can authorize the use of those reagents.

When CBER authorizes the use of reagents from other ERLs, it's expected that users have to obtain these reagents directly from ERLs. CBER recommends the use of reference antigen and reference antiserum from same source, same source meaning from a particular ERL, as what colors appear in their testing activity, and this will avoid a lot of discrepancies.

We'd like to point out that the antisera lot may need to be changed over time due to the limited amount produced per lot, and I think which I say to every year,

please we recommend that the users of the reagents please keep a small supply of your current lot, or first lot you started using, so that you can help in bridging the reagents in future.

And we strongly recommend that the same reagent -- I mean, it is desirable to use the same set of reagents for your monovalent testing, your trivalent and quadrivalent formulation, and subsequent follow-up studies, so this will avoid all of the discrepancy if you start changing reagent sources in between.

There are products being made for an alternative production platform and if there needs to be, CBER will work with the manufacturers of alternative platforms, vaccines, and try to work out the production of any specific reagents needed, or to evaluate suitability of egg- or cell-based reagents for alternative platforms.

Please do not, if I ask I you start using reagent at the start of the season, if you feel there is any problem with us please communicate with us sooner, so we'll try to work it out what is going on.

And lastly, I would like to remind that for any inquiries regarding CBER reference standards and reagents, availability, and shipping, please contact CBER Standards at the email address provided here.

In closing I want to emphasize that we at CBER are committed to make every effort to assure that reagents appropriate for all strains selected are made available in a timely manner. We also believe that making an influenza vaccine available in a timely manner is a responsibility shared by all of us here, and we all work together as a team to achieve this goal. We've been doing this year after year, and that's what we expect that hopefully we would have a good season this coming season, too.

Thank you all, and I can take any questions.

DR. EDWARDS: Thank you very much. Any questions?

DR. MONTO: Since there aren't different reagents required for something like the live-attenuated vaccine, how do you make your decisions about what reassortants and things like that, that are going to be approved for live-attenuated vaccines? I'm thinking of the A/Bolivia reassortants, which turned out not to be, to have good growth potential, as well.

DR. JOSHI: I think I would like Dr. Weir can comment about.

DR. WEIR: For live-attenuated vaccines, the suggested or the manufacturer's choice of a reassortant is actually sent to CDC and they do an antigenic analysis that it's like the recommended strain, so that's very unique to that particular manufacturer.

DR. EDWARDS: Thank you very much. Thank you.

The next presentation will be comments from the manufacturers by Dr. Beverly Taylor, the head of influenza scientific affairs and pandemic readiness at Seqirus Vaccines Limited, in the United Kingdom. Dr. Taylor?

Agenda Item: Comment from Manufacturers

DR. TAYLOR: Good morning, everybody. First of all, I would like to thank the VRBPAC committee for giving us the opportunity to give an industry presentation. So thank you very much for that.

I'm going to start off with a diagram that you have seen before just showing the timing of manufacturing and how that relates to the strain decision timing. So you can see here on the diagram that the strain selection by WHO is usually late February, four strains now. We have the quadrivalent vaccines, will be recommended, and the strain selection is based on surveillance that is carried out on an ongoing basis.

If you also look at the timeline, you can see that in order to produce sufficient quantities of vaccine, vaccine manufacturers have to start production at risk, with at least one strain. Sometimes moving to two strains.

And obviously this is strain selection dates. If they get later, the likelihood of having to move to a second strain is increased. Once we have the selected

strains, sometimes if there is a strain change, we have to produce new working seeds, which we can see here, and then we are going to produce those strains and then we get to a point in the campaign where we have the calibrated reagents available. If there has been a strain change, we need to wait for the new SRID reagents, and once we have the information of how much of the three or four strains have been produced, the last pass of the manufacturing campaign is basically strain balancing. This is really important for manufacturers, because we don't want to produce too much of one strain and not enough of another, because that will limit the number of the final vaccine doses that we can produce.

Once we have the standardized reagents as well, we can commence formulation. We can also commence our stability studies on the vaccine and then move to filling and packaging and distribution.

So this table just summarizes the timing of the strain recommendations over the last 20 years, just highlighting that since 2010 we have seen the strain decisions at WHO and consequently the VRBPAC decision being later and later, and this causes some challenges for manufacturing, because the period that we manufacture at risk is increasing with every week or even day of delay of the strain decision.

So this is the same diagram that I showed again, but I just want to show you the potential impact of a later decision. So we can see here that if that decision moves into March, all the other steps -- you know, some of the previous speakers have talked about how everything is interrelated. So if we have a later strain decision, if there is a strain change, we're later in supplying antigen for reagents, the calibrated reagents are available later, we start formulating later, and we haven't as yet seen an impact on the start of vaccination dates, but I guess the very clear message from manufacturers is if you keep squashing that manufacturing window then there will reach a point if the strain decision becomes so late that we are concerned that we will start to see an impact on vaccine supply timings.

So the graph on the left-hand side here just shows the total number of doses distributed in the United States over approximately the last 20-something years. You can see that over the years, the number of doses distributed has increased significantly, and if you look at the right-hand graph you can see the distribution of doses throughout the 2015-2016 season. So you see the vaccination starting in September and really peaking and you see that tailing off around the end of November.

Obviously, to ensure vaccine supply, we're trying to balance a number of different factors here. So we obviously want well-matched strains. There has been a lot of discussion around that today, and that's obviously a key component. But we also need to have sufficient quantities, and in the timeframe that is expected, too.

And just to comment that the number of doses distributed in the United States so far for this current season is just under 146 million doses.

So I mentioned before that manufacturers have a number of concerns about the later strain recommendations. Obviously one I've just mentioned is that manufacturers carry out a larger proportion of their manufacturing campaign at risk. This year that's around two months. As many manufacturers have to start manufacturing in January. If the strains manufactured at risk are not recommended and if manufacturers have moved to a second strain manufactured at risk, that risk increases.

Then the only -- it's not only an impact on the manufacturer to discard those batches, but also we never recover those manufacturing slots. So if we have manufactured the wrong strain at risk, then we have potential resource limitations and we will be trying to catch up for the rest of the campaign, which could again

impact the timing and the quantity of the vaccine available.

The other additional pressure, as you saw in the previous graph, the number of doses distributed in the United States has increased significantly. So that means that that is even more pressure. So we are not talking about a lower number of doses here. We are showing an increase in the number of doses being distributed, and if there is a later strain recommendation, that manufacturing window being more and more challenged, and we feel that all these different components added together are significantly increasing the risk of delaying the vaccine available.

Obviously for this year for WHO, they did not change the strains from the southern hemisphere. So maybe we would not see something in this particular season, but for future seasons, if there were to be strain changes, this could have an impact.

So we have had many discussions. HHS BARDA held some mismatch meetings in 2015, and out of that they have developed their seasonal influenza improvement initiative, and there are many suggested improvements to have representative virus or CVVs identified early. Really push for high growth reassortants and perspective -- the perspective yields known ahead of time. This includes non-frontrunner viruses. So if we were to see, you know, we

can see for some of the strains of virus that it's quite a complex genetic picture.

So something that seems like a non-frontrunner virus, that could change very quickly. So if we also had CVVs for those we would be able to respond much more quickly. Also preparing more antigens and critical reagents for more of the candidate vaccine viruses at risk so that we have those earlier.

However, I think the key message here is there has been a lot of discussion about this. There's a lot of good work planned, but we are not there yet, and these improvements really need to be in place if we are going to see the benefits of them.

So what do manufacturers do to prepare as much as possible for the influenza campaigns and particularly around the northern hemisphere 2017-2018 season. So we track surveillance data through summaries of internal WHO TCs that are held to look at the surveillance data, and they now include a table at the end of that summary, which lists out all the viruses of interest. So that gives manufacturers an idea if there is a new area of interest or there's a particular virus that is of increasing interest.

We use websites such as the WHO FluNet and CDC FluView to look at the surveillance. Again, we do the best that we can with the data, but it's not always a clear

picture. You know, if you look at the B strains this year, you can see the B/Victoria overall over a period of time is higher, but some weeks it seems to be B/Yamagata higher. So it is really not always clear.

We also track the availability of candidate vaccine viruses for manufacturing through the WHO chaired technical TCs, which are held every two weeks, and for this year the ones that we started for the southern hemisphere, we actually continued right up to the northern hemisphere strain recommendation to give us more information on surveillance for the northern hemisphere.

And also we now have a spreadsheet of viruses of interest and what stage of preparation they are at. This is really for the high growth reassortants. This spreadsheet was developed between NIBSC and the Crick Institute in the UK. It's really in its infancy. We have only started using it in the last few weeks, but the idea is that this will provide timely updates on the development status for the new strains that will be available for manufacturing, and ultimately we hope to get that as a real-time tool that we could log into at any time and see what the status is.

And industry also closely engages with the WHO and U.S. agencies at multiple forums. If you just look at the -- so the line in the middle is sort of the calendar

running from one VRBPAC meeting to the other. Here, if you look at the lighter blue squares, there are some really key dates in our calendar where we get detailed surveillance information. So if you look here, we have an NIBSC meeting in July. We have a BIO-FDA Flu Review in December, and we have another NIBSC flu review usually held either late January or early February, and they're key opportunities for us to really understand the surveillance and what candidate strains are available and where reagents erupt to. So they are really key meetings for us.

We also have a host of other meetings that we are involved in, and we have industry representatives attending. So we do work very closely and collaboratively to resolve issues, to get updated information. We are working together to improve influenza vaccine supply, pandemic preparedness, and I hope that this slide really illustrates how closely that we're working with the agencies.

So this slide is just giving an overview of some of the strains which have been evaluated for the upcoming northern hemisphere season. So based on the WHO recommendations made last week, these -- so the WHO recommended like strains are in red on the slide, and the candidate viruses are listed underneath. So these are what manufacturers have been evaluating for the upcoming season.

So that concludes my talk about the preparations for the upcoming season. I just want to switch gears a little bit and mention the Nagoya Protocol. Again this was raised last year during the industry presentation, and it's something that we continue to be extremely concerned about. So just a brief reminder. The Nagoya Protocol was developed from access and benefit sharing discussions at the Convention on Biodiversity, which was adopted in 2010. It came into force in October 2014, when the 50th company ratified the Nagoya Protocol.

So the objectives are to ensure access to genetic resources and related traditional knowledge for potential use and ensure that users and providers of the genetic resources and related traditional knowledge agree on fair and equitable sharing of benefits arising from their use. It is important to point out that this came through the agricultural routes, the environmental routes, rather than the public health routes, but it obviously covers viruses. Many countries are including pathogens in the legislation that they are developing around Nagoya, and we are concerned that this will cause delays in supply viruses for a seasonal vaccine manufacturing.

So there have been some key developments this year. So WHO carried out a review in 2016 to look at the potential impacts on public health of the Nagoya Protocol,

and the WHO and the CBD are being encouraged to identify and develop means to mitigate the potential impact of Nagoya obligations on the sharing of influenza strains, because under Nagoya companies would have to negotiate bilateral agreements with the supplying country, which could cause significant delays and we have previously estimated that this could be up to three months delay in receiving or having the ability to move forward and work with the strains.

Industry does support escalating both the WHO GISRS system as well as the PIC framework to something called specialized international instruments for access and benefits sharing. What this would do would be if they were recognized under the Nagoya Protocol, then both seasonal and pandemic influenza viruses would become exempt from time-constraining Nagoya obligations in the future. We heard from WHO last week that there is a meeting in Montreal, the third week in March, where they will be working with the CBD secretariat to develop a process through which to identify specialized international instruments. So that is like the first step forward, because currently there isn't even a process under Nagoya to recognize these specialized instruments.

The United States is not a signatory to Nagoya. However, we are not sure of the potential impact on

influenza vaccine availability in the United States, because there could still be some restrictions through the Nagoya Protocol.

Just to make the point, the next slide shows from the previous slide when I listed out all the candidate vaccine viruses being considered for the upcoming season, I have crossed out all the vaccines that come from Nagoya signatory countries. Scotland is still on there. The UK is a signatory but has waived their right to benefits through Nagoya. So that remains on the list.

And this is the potential impact. It depends on the local legislation and whether pathogens have been covered by the local legislation in those countries, but I just think that this slide is quite powerful in showing the potential impact that we would have, because it could vastly reduce our choice of viruses, which could reduce our ability to find a well-matched virus for the seasonal influenza vaccine.

So in conclusion, the timing of strain selection and vaccine supply requires close collaboration between multiple stakeholders to ensure sufficient provision of vaccine each season. This season we are as manufacturers going through our preparedness -- our preparedness is ongoing. However, we identified future improvements that could help us respond more quickly and react more quickly

to changes and maybe mitigate later strain recommendations, but I think it's very clear from our point of view any delay in the strain recommendation would potentially cause a delay in vaccine supply.

And then the final point is that adherence to the Nagoya Protocol could result in delay in influenza vaccine supply. We know that WHO and CBD are collaborating to identify ways of mitigating this, but it still remains a significant concern for manufacturers.

Thank you very much for your attention.

DR. EDWARDS: Thank you. Are there any questions?

DR. SCOTT: I have a question on how do you choose the strains that you do at risk before -- is it across the same across all the companies, or does each company just choose one strain or two strains that they do at risk?

DR. TAYLOR: I think usually based on the surveillance, there is usually one virus that is -- you can never say it's never going to change, because in 2008 we had three strain changes, but it's least likely to change, and I think that the majority of manufacturers would choose that strain. So for example, for this year, the H1N1 pdm09 virus was probably the least likely to change. It was very unclear with the H3N2s. For the quadrivalents, the Bs were clear, because the Bs for each lineage, the strains weren't

changing, but for manufacturers still producing TIV, which B was going to predominate really has not been clear.

So I think the majority of manufacturers may have chosen H1N1 this year. There's usually a clear frontrunner for the strain to run at risk. Where we come into difficulties, if the strain decision is delayed, manufacturers may have produced enough of that strain and have to switch to a second strain which is not so clear, and that would increase the risk.

DR. BENNINK: From your slides, is all of the manufacturing done by September or something like that for the current season?

DR. TAYLOR: I would say for the majority of -- I can't speak for every manufacturer, but I would say the majority of manufacturers, all manufacturing is completed by September. There may be still some filling in, packaging activities, ongoing.

DR. EDWARDS: Thank you very much. We are running a trifle behind. So I think we will have 45 minutes for lunch. We can come back at 1 o'clock and if you want to -- if you need longer than that to complete your meal, you can bring it back here, but we will start at 1 o'clock. Thank you.

(Lunch recess.)

Afternoon Session

Agenda Item: Open Public Hearing

DR. EDWARDS: For public hearing, are there any individuals who would like to speak?

(No response.)

Agenda Item: Committee Discussion, Voting, and Recommendations

DR. EDWARDS: If not, then I think we can get to our committee discussion, voting, and recommendations.

Do we want to put up the voting questions, or do we all have them? We could do that. Could we do that? Just put the voting questions up on the slide?

Okay, I'd like to open the discussion for concerns and discussion around the first question, the composition of the trivalent vaccine, thoughts, concerns, committee?

DR. WHARTON: Thank you. My understanding from the presentations is that it appears that the situation in North America for Yamagata versus Victoria may have been a little different than for other parts of the northern hemisphere, and I wondered if Jackie or Lisa could confirm if that's correct.

DR. KATZ: So based on the data we had available for the vaccine consultation meeting last week, both Europe and North America were seeing slightly, like 54, 56 percent

B/Yamagata, and 46, mid-40s percent of B/Victoria, but it was pretty close.

For Central, South America, and obviously there's less data from them also, and Asia and Africa, they definitely saw more B/Victoria in the period we were looking at. Oceania, which is largely a lot of Australian data, they had quite a swing to B/Yamagata in this season.

DR. EDWARDS: The B that is currently circulating sort of in the tail of the strains this year then would be about equally distributed between the two strains in the United States, or do you have enough data to say?

DR. KATZ: It's probably changing week by week and certainly I think as there's been an upswing in Bs, there is a little bit more B/Yamagata.

The data that I'd put into this table, to the pie charts that I showed you, is our most recent data. So you can just see that month by month, it sort of is cycling up and down, but currently in the United States, yes, I would say B/Yamagata is edging out B/Victoria.

DR. WHARTON: Well, of course this is exactly the reason why this committee, several years ago, started talking about the benefits of including both B strains and annual influenza vaccination, which we are doing to an increasing degree in the United States, but we do still market trivalent influenza vaccines -- we still do market

and use trivalent influenza vaccines in the United States and I'm very conscious of influenza vaccination being a global enterprise where companies manufacture vaccines for use in multiple countries.

I hate asking this question, but I'm going to ask it. If we were to select a B strain that differed from the WHO recommendation, would that adversely impact vaccine production for the U.S. market? I'm not sure who this question is directed to.

DR. EDWARDS: Perhaps Dr. Greenberg?

DR. GREENBERG: I don't have a direct answer to the question, primarily because I don't know what each of the manufacturers have done with regard to the strain or strains they're producing at risk because I'm speculating a bit, but of course my colleagues in the audience can be specific. But if, for example, a manufacturer is not manufacturing one of these strains right now, then I'm not sure that it would make any difference, but I'm sorry; I don't have a direct answer.

DR. WEIR: Just to follow up on that, this is really sort of a question for the manufacturers obviously, but it seems like one impact could be for manufacturers who are making vaccines worldwide, and if the formulation of a trivalent is different for the United States versus somewhere else, and I don't know how many companies that

would affect. I mean, you'd have to almost poll individual companies and find out.

DR. EDWARDS: The high dose influenza vaccine, that's still a trivalent, correct? Is that planned to be a quadrivalent?

DR. GREENBERG: Do you want me to answer that as the industry representative, despite the fact that I know -- it's a little bit out of turn or place, but I'll answer. It is a trivalent and there are clinical trials taking place to move that to a quadrivalent.

DR. JANES: Dr. Katz, you mentioned the modeling work predicting the future circulating strains and the difficulty of doing that, but can you make any comment on what those projections have done to inform the WHO recommendations and how it relates to the Yamagata versus Victoria?

DR. KATZ: No, in fact, one group just only really addresses the H3N2s since that's our most problematic one. The focus really is within a lineage for the Bs, which, is there is genetic diversity, what is likely to take off? So I can look back on the package, but I don't recall they made predictions about which lineage would take over.

As we've said, it varies by region in the world, and it's quite dynamic and different. It's going up and down all the time with respect to the proportions of B.

DR. MONTO: The group at Cambridge, and I think that their approaches have been published, have suggested a variety of approaches such as just alternating the strains and trying to anticipate which way things are going.

Given the fact that the whole world is not going to quadrivalent vaccine, is it time to revisit those issues? Because it seems like one of the reasons we want to quadrivalent was because of the inability to predict, and that inability to predict is still present.

DR. MCINNES: So we've discussed this for years. It's had a Yamagata year followed by a Victoria year followed by a Yamagata year, right? So I had a question. Given that we're concerned about infants and children which regard to B, are there any data about what U.S. children are getting with regard to trivalent versus quadrivalent?

DR. WHARTON: Well, I think we can identify what we buy for the public-sector program, which, off the top of my head, I don't know.

DR. GREENBERG: I don't have much to add, just to say that it is difficult to track because for the most part, influenza vaccines are not age-specific, so then therefore it's difficult to track which of the vaccines get into children of most ages. There are of course some exceptions to that, but for the most part, it's hard to know which vaccine gets to which age group.

DR. EDWARDS: Any comments or perhaps, Patrick, do you want to bring up your H3N2 concerns again, so we can ponder those again?

DR. MOORE: I am concerned. Well, I think that I am not convinced that the Hong Kong strain is going to be any better next year, but unfortunately I don't see any evidence that there is another strain that is better than Hong Kong.

Also, the other thing I would reiterate is that the data looks very interesting in terms of whether there is a cell-based versus egg-based difference in antigenicity for the vaccine based on the ferret data. Whether that pans out I guess we'll know, but certainly we should be very focused on finding out whether there is a cell-based vaccine efficacy that's different from the egg-based vaccine efficacy for the H3 strains in the upcoming year.

DR. MONTO: The problem is, how do we find this out? With the vaccine effectiveness studies, which are the only ways we can find out on an annual basis what's going on, the problem is that not enough of the cell culture-based vaccines being used in the United States to be able to say that it's better, and there's no likelihood that this is going to change. Again, we need more evidence for exactly what's going on based on what we know. We think

that the egg adaptation is one of our many problems with the H3N2 vaccines.

DR. MOORE: Is there any evidence for another candidate strain that would be better than Hong Kong, particularly a 3C.2a1 strain that would be more closely related to the centroid of the genetics of the new viruses that are coming out?

DR. KATZ: So the analysis that the collaborating centers did include some more recent viruses. Of course, the question is there's 3C.2a1 viruses of which we have many that are grown in cell culture that are being characterized, but few of them have been isolated in eggs exclusively because that's another challenge, that 3C.2a1 viruses are being a little more difficult to isolate in eggs.

But we had one candidate at CDC that's very poor, and the other two are just unknowns at this time. They're not at the stage where we could hand them over to manufacturers and that's not likely to be -- they're still in development as candidate vaccine viruses as far as I'm aware at different laboratories, and then it would take quite some time to do characterization and really evaluate how well they're reacting compared with circulating viruses.

I mean, the antigenic studies we've done says that the 3C.2a1's, although genetically they're different, that antigenically, 3C.2a1 Hong Kong/4801 covers those viruses quite well, and we don't have a good 3C.2a1 candidate that has been evaluated to any extent.

DR. BENNINK: Another one that is not very broadly, probably, as used as the protein science is the recombinant version of theirs. Is that being tracked in efficacy at all as separate from the others?

DR. MONTO: It is the same problem. If not enough is used, you don't have a sufficient sample size. We do have this year, probably, results which might be useful for the high dose, but that's only because a lot of high dose is currently being used in that age group.

DR. EDWARDS: Certainly those are important questions, whether those could be generated into funding opportunities to address those questions or to specifically add vaccines into your study. I don't know whether that's an option either.

DR. MONTO: I think there are options to enrich the use of certain vaccines in certain population groups. I think it just takes planning and attention.

DR. EDWARDS: It seems like that the H3N2 we've sort of addressed and I think we, perhaps, I truncated the B discussion a little bit too quickly. Hana, you had

brought this up originally, do you have some thoughts about one B as opposed to another B, to be or not to be?

DR. EL SAHLY: Ideally, I would think two B, but if the pattern of 50/50 is going to continue, or 40/60, to me, the difference doesn't seem that big, and I don't know how this suggestion would impact delivery of vaccine, manufacturing of vaccine, which are at times more important considerations alternating seasons, but the impact on public health in terms of delivery and manufacturing would also have to be considered.

DR. EDWARDS: Any comments on H1N1? Are we ready to vote or do we have some other comments? Go ahead, Patrick.

DR. MOORE: This is not a strain-specific comment, but it is based on the presentation this morning with the vaccine timeline. Can I make a comment or do you want me to do it later?

So the industry representative made a valid point this morning, that the supply timeline is very problematic with late VRBPAC and WHO meeting dates and how to resolve that because we really need -- there's a pressure to move the dates to later, as late as we can get them so that we can get more surveillance data which is critical for us making a good decision, whereas having that decision

earlier is good for industry to be able to make the vaccine. Both of them are important things.

One possibility, and I just raise this, is that it may be valuable for FDA to start discussions with CDC and WHO in order to try and resolve this, to try and push the VRBPAC dates to an earlier date, perhaps late February.

Or alternatively, one suggestion would be to reserve for the committee two separate dates, one in, say, early- to mid-February, and one early March, and have CDC be able to tell us which, if there is a new strain that's emerging in January and February that obviously might impact the strain decisions, they could tell us which date they need to have surveillance data accumulate by the time they could present. It's just an idea for trying to resolve this practical problem.

DR. MONTO: I remember a few years ago when the VRBPAC met before, because of logistic considerations, before the WHO's strain selection meeting, and it was futile as they say because you couldn't really do anything.

DR. MOORE: Can we or can someone, meaning FDA, CDC, approach WHO to try and move back their date or at least try and coordinate it?

DR. KATZ: Yeah, after we had discussion with industry, WHO is aware. They will consider, so the global influenza program at WHO sets those dates, and there are

multiple factors that play into it, but I think as we discussed with industry last Thursday, there is the desire to keep it maybe not as late as it was this year, but which was, I'm not sure why, but I think it was just the way the calendar fell.

But recognizing that we don't want to be pushing this into March, but we still are most likely not going to move it back to where it was 10 years ago where it was sort of more consistently mid-February. We need some middle ground there to really get the best and most data we can for the decision-making process. So we heard industry loud and clear, and it will be up to the global influenza program to make that decision for next year.

DR. JANES: Back on the B lineage question, is what I am hearing correct that that the main consideration not to consider swapping out the B in the trivalent vaccine is manufacturing considerations, or are there scientific reasons not to do that that I haven't heard?

DR. KATZ: I guess at least this year, it looks like about 70 percent of the influenza B/Victoria infections are in persons under the age of 25. So it's affecting children more heavily. So if children, some children, are only getting TIV, maybe that's a rationale for keeping B/Victoria.

I think when WHO has alternated, I mean, they were on a cycle maybe about seven or eight years ago where they were alternating and it seemed like they just kept missing it. They were like, one season behind, and I don't know, we really can't predict what's going to happen except the current circulation of Bs worldwide suggest that both of them are quite comfortable, both lineages are both circulating quite comfortably, and one isn't sort of competing out the other at this time. Certainly that seems to be, and everything was at a low level.

The other thing to realize is I don't think we've had an exclusively B season for a long time. B's always a part of the strains that circulate and may not even be the dominant one as we've seen with H3s and H1s dominating in recent years.

DR. MCINNES: Somewhat lighthearted, but I am reminded of the great Rob Webster. He used to stand and say, if only I had a crystal ball. So it's that situation, right?

DR. KOTLOFF: I just want to clarify again how global our recommendation is supposed to be. If I'm looking at the right data, I mean, we're talking about 75 to 80 percent of the Bs in Africa and Asia, which are much more populous than Europe and America, although I don't know what the number of vaccines given is like, or

Victoria, whereas we're talking of very close, it's like 40/60 in the opposite direction in Europe and North America. So should our perspective be the number of people worldwide, the number of vaccines that are administered worldwide, or just the United States? What are we answering for?

DR. EDWARDS: Jerry, do you have wisdom about our jurisdiction?

DR. WEIR: No, not really. This is not a new problem in some ways. The committee is clearly supposed to make recommendations for the United States. How you weigh all of the data worldwide is the problem, and you're trying to predict are strains that are circulating in one region like Africa going to be the ones that circulate more next year, or the ones in some other part of the world? I don't have an answer for that.

DR. MONTO: I will say something which I was not planning to say, and that is, what would the consequences be if we made a decision, given the fact that influenza vaccine is a global commodity, that was not in agreement with the recommendations of the WHO? How would the manufacturers, David, respond to something like that from a practical standpoint?

DR. GREENBERG: Well, I think that these sorts of questions do have to go to the individual manufacturers as

to whether or not there's going to be any impact on which B lineage goes into the trivalent and quadrivalent vaccines and what impact that would have on manufacturing and supply. I think that in the end, obviously, the vote of this committee then is how CBER licenses each manufacturer's vaccine.

So when you ask, would it matter in terms of the recommendation to WHO, from a manufacturer's standpoint, it's kind of agnostic because whatever you all decide is what the manufacturers must do. But I can't answer the question. If you want more detail about what a decision opposite of WHO would have on the manufacturer's process and the supply and timing, I think each one needs to be asked.

DR. WEIR: Just to clarify, this is not a regulatory question. I mean, manufacturers would just follow the recommendation and submit the same supplements they always do. So if there's a question here, it's really for manufacturers.

DR. BENNINK: Jackie, do you know, you gave us a percentage under 25 of 70 percent or something like this, do you know what the over 65 is, since that's a trivalent?

DR. KATZ: Well, not all the over 65s are getting high dose. They could get standard which could be QIV. I'm just looking at, if I can find it again, this is just

reading off our week 8 FluView, and it looks like in the 65 and older age group, so for those infected with B/Victoria lineage, it's a small proportion of those over 65, it looks like it's sort of less than 10 percent.

So the older age group isn't really getting that affected by B/Victoria this season. It's more like 25 percent for the B/Yamagata lineage. The B/Yamagata lineage is sort of more like, the age distribution is a little more like the influenza A distribution. Did you have that? You had on your slide, didn't you, Lisa, this age breakdown? Oh, you didn't present that.

So it looks like in the older age group for this season in the United States, that they're not heavily affected with B/Victoria, and if they got B, I guess there's a greater proportion of that age group that had B/Yamagata.

This is, again, only where we have that lineage breakdown, because there's some Bs that we don't have lineage determined for.

DR. JANES: There would be some protection for individuals who were previously vaccinated with the B/Victoria lineage and my question is what do we know about the durability of those immune responses and what those would predict about their protection this year if they were vaccinated with a different B?

DR. EDWARDS: The granularity of your VE data, in terms of the B, can you comment on that, Lisa, on how effective the trivalent vaccine was for the B strains?

DR. GROHSKOPF: Not specifically for the trivalent because those data weren't broken down by the trivalent and quadrivalent, the B figure that was presented as overall and actually was not even broken out by age. Was that the question, whether the trivalent --

DR. KATZ: Right, but overall, or for B/Yamagata specifically, it was like 70-ish percent.

DR. GROHSKOPF: Right, 70-ish percent, and even though those weren't broken down by lineage, again, only 1 percent of the total isolates were for the B data thus far were Victoria. So essentially that's a figure for Yamagata.

DR. KATZ: That's in those sites, they had more B/Yamagata than B/Victoria.

DR. JANES: But understanding that the VE data are sparse and just looking at immune responses that these vaccines generate, how durable are those?

DR. GROHSKOPF: In terms of immunogenicity data, if we're speaking of durability of immune response, my understanding of that literature is most of it examines durability for flu A, and there's a lot of discussion and a

good number of papers for the last few years for waning of immunity, particularly in the older population.

When waning is observed, it's mostly been observed for H3, but I don't think there has been, and there are probably some people here who may know more about this than I do, most of what's been observed is in the H3, not so much the H1, but I don't think the literature database is as rich for B as far as durability of response from season to season particularly in older people.

DR. MONTO: Yeah, the problem with B serology, the fact that if you don't use either split antigens, you see lower responses by far to B in the HI test has led us down the garden path to think that our B vaccines weren't working.

With this 1 to 40 magic amount that was supposed correlate with protection, we still have the same problem. One of the revelations from the vaccinate effectiveness study is that the B study has consistently outperformed the A(H3N2) vaccine, and we have less to worry about. Not only that we have some evidence at least in adults that there's cross-protection between the lineages. So it's really, our big issue is H3N2 right now.

DR. WEIR: Can I follow up with what Arnold just said? Does that mean you would place somewhat greater

weight on what might happen with children for the selection of the B strain?

DR. MONTO: The problem again is we've had relatively small numbers so we can't even say what a cutoff would be in young children. Certainly from studies that were done years ago where they were trying to give the two doses, one in the spring and one in the fall, it looks like it makes a difference with young children in terms of the lineage, but whereas, and these are very young children who are getting initial vaccinations. I think the history of infection also falls in there and that's the thing that, without longitudinal studies, you can never figure out.

DR. KOTLOFF: I needed some clarification. I was just wondering, if you're looking at severity of disease, if there is a greater representation of either of the B strains. So I was wondering if there were any data on deaths and then I went back to this slide in Lisa's talk, the second slide that looks at hospitalizations, but the key is missing, at least on what I have here, to know which -- I think the green colors are the Bs but I can't tell which is Yamagata and which is Victoria.

DR. KATZ: They are the green. Do you know which is the lighter green?

DR. GROHSKOPF: I believe the darker green at the base is the Yamagata, but I will check that and confirm it right now, actually, because I think I can do that.

DR. KATZ: So the very dark green, which is at the top of the green bars, is the Yamagata. Oh, hang on, no, sorry, the darkest green is B lineage not performed. The next one down, which is sort of the brightest, palest green, is B/Victoria, and the bottom one, which is that intermediate green, is the B/Yamagata. So that's showing in recent weeks there's more B/Yamagata than B/Victoria.

DR. KOTLOFF: Do you know anything about the deaths?

DR. KATZ: I think, Lisa, do you want to talk about how we don't have subtyping on the virus information on the deaths?

DR. GROHSKOPF: We don't have, at least pediatric deaths, we don't have subtyping or AB information on all of the deaths. For the current season deaths, it's reported in the most recent review that there were two H3N2s, one H1N1, two unsubtyped and one B, but we're dealing with a relatively small sample size of one week there.

DR. KATZ: But each week it's been distributed, sort of H3, B, there's no predominance that the pediatric deaths are attributable to B, I would say.

DR. MONTO: Isn't there also a problem about regionality with any of these? We're legislating for a very large country, and there's going to be variation in one region over another, especially with these. It can be very different.

DR. GROHSKOPF: Correct, and again, I had mentioned in the summary to the surveillance presentation that in recent weeks, it appears nationally things are starting to level off in terms of activity, but if you were to look at different regions, it's not the same across all regions. There's some where it may still be increasing, some where it may be starting to plateau and decrease. So we do have to, that's an excellent point, we have to keep in mind that things aren't going to be the same in every region in the country. The predominant viruses won't be the same in every region of the country necessarily. So that's an important point.

DR. GREENBERG: I just thought I'd add a comment since there's a lot of focus on B and children, and I commented earlier that you don't always know which of the vaccines get into each age group.

But I will say that, and I think I'm speaking correctly here, if I'm wrong, someone corrects me, that's fine, but I think in general, a few years ago when quadrivalent vaccines began to come onto the market from

the various manufacturers, for the most part, pediatricians thought that that was the right thing to do. The children were probably going to be more susceptible to one lineage versus another if it wasn't in that trivalent vaccine during that season, and really they accepted the logic.

Although I don't know exactly what percentage of children received quadrivalent versus trivalent, there are still trivalent vaccines that are on the market, so some do. But I think that in general, most children receive quadrivalent because most pediatricians have accepted that as the proper vaccine to give in that age group.

DR. EDWARDS: I think also prior to that time, there were some papers that looked at predictions, not quite exactly what Jackie was saying with WHO and trying to predict, and by and large, it was like flipping a coin in terms of predicting. So I think that was clearly the case. So it was problematic.

DR. KOTLOFF: Is there any mechanism or way to get the message out, particularly for children, that quadrivalent would probably be a better bet because of their Victoria distribution?

DR. EDWARDS: I think certainly that's what the COID from the AAP tries to do, and so I think that has been a message that's consistently been preached by the pediatricians and certainly is a reasonable one.

Okay, why don't we go around and then make any last comments before we vote? Let's start with Pam. Are there any things that you would like to bring up before we vote or any thoughts that you wanted to share?

DR. MCINNES: I'm pleased to hear about the pediatricians, because that was what my question, I was trying to get at what percentage we think kids are getting, given that that's the population I'm concerned about with regards to this conversation in B. So that was helpful. Thank you. No, nothing else.

DR. WHARTON: I guess several years ago we realized we were not able to predict what was going to happen with these strains and so it is, cognizant to the fact that what I'm about to say is probably wrong, that if we were to make a decision about a B strain, only based on U.S. surveillance data and without considering anything else, I would personally advocate for considering making a change to the Yamagata lineage.

But that is not the case. The case is we are in a country that uses vaccines manufactured by multiple global companies, and I'm concerned that a change would adversely impact the availability of vaccine in the United States, and given that so much quadrivalent vaccine is already being used, and a lot of that, I don't know how

much, in children, it does seem like the risks of making that change may very well exceed the benefits.

DR. GREENBERG: I didn't have a comment, but from Melinda's comment, I'd like to just acknowledge that it didn't actually click with me until you just said that that absolutely, and so as representing industry, I think what you said makes a lot of sense because there are -- and again, I invite people from industry from the audience to comment further, but you're right. There are manufacturers that make vaccines in either a single or limited number of manufacturing sites, and their vaccines are distributed globally.

So to the extent that this committee's recommendation might be different than WHO, you're right, that could have major impact.

DR. EDWARDS: That would be a confusing message as well, exactly. All right, I think then we are ready to vote. The first question is for the composition of the trivalent 2017.

DR. WEIR: Can we vote on these one at a time?

DR. EDWARDS: Yes, please. So the composition of the trivalent 2017-2018 influenza virus vaccine in the United States, does the committee recommend the inclusion of A/Michigan H1N1-like vaccine? Yes or no?

DR. ATREYA: Before you vote, there are three buttons on the voting machine, the microphone, and so this voting should be simultaneous and after you vote, then the results will be computed and then will be projected and then I will have to read them aloud for the public record. Thank you.

DR. EDWARDS: So this one is A/Michigan H1N1. Vote.

DR. ATREYA: Dr. Scott said yes. Dr. Stanek said yes. Dr. Bennink said yes. Dr. Wharton said yes. Dr. Monto said yes. Dr. Moore said yes. Dr. Edwards said yes. Dr. El Sahly said yes. Dr. Janes said yes. Dr. Kotloff said yes. Dr. McInnes said yes. So there are 11 or 12 -- 11 unanimous.

DR. EDWARDS: So the next question will be for the 2017-2018 influenza vaccine to include A/Hong Kong H3N2-like virus.

DR. ATREYA: Okay, again, Dr. Scott voted yes. Dr. Stanek, yes. Dr. Bennink, yes. Dr. Wharton, yes. Dr. Monto said yes. Dr. Moore abstained. Dr. Edwards said yes. Dr. El Sahly said yes. Dr. Janes said yes. Dr. Kotloff said yes. Dr. McInnes said yes. So there are 10 out of 11 said yes, and one abstention.

DR. EDWARDS: Okay, the next vote will be for the trivalent 2017-2018, the inclusion of the B/Brisbane Victoria-like lineage.

DR. ATREYA: Okay, once again, Dr. Scott said yes. Dr. Stanek said yes. Dr. Bennink said yes. Dr. Wharton said yes. Dr. Monto said yes. Dr. Moore said yes. Dr. Edwards said yes. Dr. El Sahly, she abstained. Dr. Janes said yes. Dr. Kotloff said yes. Dr. McInnes said yes. So it's 10 out of 11 votes for this question.

DR. EDWARDS: Thank you. For the final question for the quadrivalent vaccine, does the committee recommend the inclusion of B/Phuket in the vaccine?

DR. ATREYA: Okay, once again, Dr. Scott said yes. Dr. Stanek said yes. Dr. Bennink said yes. Dr. Wharton said yes. Dr. Monto said yes. Dr. Moore said yes. Dr. Edwards said yes. Dr. El Sahly said yes. Dr. Janes said yes. Dr. Kotloff said yes. Dr. McInnes said yes. So there are 11 out of 11, unanimous.

DR. EDWARDS: So I think we have accomplished our task today and thank you, everyone, for your participation for the members and the guests, and hopefully we have chosen the right strains.

(Laughter.)

DR. ATREYA: Thank you all very much for your participation. I appreciate it. This closes the meeting. Meeting is adjourned.

(Whereupon, at 2:00 p.m., the meeting was adjourned.)