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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
(CBER)

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE (VRBPAC)

137TH MEETING

WEDNESDAY
MARCH 4, 2015

The Advisory Committee met in the DoubleTree by Hilton Hotel, Pinnacle Ballroom, 8727 Colesville Road, Silver Spring, Maryland, at 8:30 a.m., Robert Daum, Chair, presiding.

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PRESENT

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SCOTT STANEK, D.O., M.P.H., Temporary Voting Member
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FILIP DUBOVSKY, M.D., M.P.H., FAAP, Temporary Voting Member and Acting Industry Representative
JACQUELINE KATZ, Ph.D., Temporary Non-Voting Member and Speaker
ANISSA CHEUNG, M.Sc., Speaker
MICHAEL COOPER, Ph.D., Speaker
MARION GRUBER, Ph.D., Speaker
MANJU JOSHI, Ph.D., Speaker
SAM LEE, Ph.D., Speaker
JERRY WEIR, Ph.D., Speaker
ZHIPING YE, M.D., Ph.D., Speaker

ALSO PRESENT

SUJATA VIJH, Ph.D., Designated Federal Officer
DENISE ROYSTER, Committee Management Specialist

TABLE OF CONTENTS	Page
Call to Order and Opening Remarks Robert Daum	4
Conflict of Interest Statement Sujata Vijh	4
Introduction of Committee Robert Daum	10
TOPIC: STRAIN SELECTION FOR THE INFLUENZA VIRUS VACCINES FOR THE 2015-2016 INFLUENZA SEASON	
Introduction Anissa Cheung	15
U.S. Surveillance Lisa Grohskopf	26
World Surveillance/ Virus Characterization Jacqueline Katz	63
DoD Vaccine Effectiveness Report Michael Cooper	108
Vaccine Responses Zhiping Ye	131
Candidate Vaccine Strains and Potency Reagents Manju Joshi	147
Comments from Manufacturers Sam Lee	159
Open Public Hearing Robert Daum	169
Committee Discussion, Voting, and Recommendations Robert Daum	209
Adjournment Robert Daum	237

PROCEEDINGS (8:33 a.m.)

CHAIR DAUM: Would everyone take their seats? Thank you.

I would like to welcome everybody to a VRBPAC meeting. We all remember what each other looked like, since we haven't had one for a while. But I would like to turn the floor over to Dr. Vijh to make the introductory comments and the conflict of interest statement. Dr. Vijh.

DR. VIJH: Thank you, Dr. Daum. Good morning, everyone. I am Sujata Vijh, the Designated Federal Official for today's Vaccines and Related Biological Products Advisory Committee meeting.

Ms. Denise Royster is the Committee Management Specialist and Ms. Joanne Lipkind is also assisting her today with this meeting.

On behalf of the FDA and the Center for Biologics Evaluation and Research, I welcome everyone to this 137th meeting of VRBPAC. Dr. Daum is the Chair of VRBPAC. Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the *Federal Register* Notice of December 22, 2014. The FDA VRBPAC CBER Press Media Contacts, Ms. Tara Goodin and Mr. Paul Richards, if you are in the audience, could you please stand up? They are right there. And any members of the press that may be present should contact them for additional information.

Mr. Toby Walter is the transcriptionist right here. So, he will be looking out for you to be speaking into the microphone so he can capture your notes.

I would like to also welcome two new members to the panel. Dr. Kathryn Edwards is right here and Dr. Ofer Levy right there. Welcome to the panel.

This is my first meeting, so I am meeting everyone for the first time. So, I am trying to connect the faces with the names.

So, I would like to request you to please check your cell phones and pagers to make sure that they are on silent mode or on vibrate so that they don't disrupt the meeting proceedings.

For the members sitting at the table, when you speak, please press the microphones and the red light comes on. Please speak into the microphone loudly and clearly so that your discussion can be heard by the transcriptionist, by members of the audience as well as members of the public listening on the webcast.

And at any given time, there should be just four microphones on; otherwise, the sound gets cut off. So, after you have finished speaking, please switch off the microphones.

Just a few logistics. You might have already found out that the restrooms are outside. There is a cash coffee bar outside plus there will be a lunch buffet in the restaurant downstairs for purchase. So, just a few logistics to make you comfortable.

I will now read the conflict of interest statement for the meeting for the public record.

The Food and Drug Administration is convening today, March 4, 2015, for a meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S. Code Section 208 have been provided to the participants at this meeting and to the public.

The FDA has determined that all members of this advisory committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have

financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

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

For the topic today, March 4, 2015, the committee will discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2015 to 2016 influenza season. This is a particular matter involving specific parties. Based on the agenda and all financial interest reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code Section 208.

Dr. Filip Dubovsky will serve as the alternative industry representative. Dr. Dubovsky is employed by MedImmune, LLC, Gaithersburg, Maryland. Industry representatives act on behalf of all related industry. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have

financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

This conflict of interest statement will be available for review at the registration table outside.

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.

FDA encourages all participants to advise the committee of any financial relationships that they may have with any firms, its products, and if known, its direct competitors.

This concludes my reading of the financial conflict of interest statement. Dr. Daum, I hand over the meeting to you.

CHAIR DAUM: Thank you, Dr. Vijh.

What I would like to do is go around the room and do the obligatory identification of ourselves so that anybody watching or listening or anything can know who we are. Jerry, do you want to start?

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

CHAIR DAUM: We can go right down the table here.

DR. GRUBER: Marion Gruber, Director Office of Vaccines, CBER FDA.

DR. LEVANDOWSKI: Roland Levandowski. I am an independent infectious diseases physician from Bethesda.

DR. ENGLUND: Janet Englund, Professor of Pediatrics, University of Washington and Seattle Children's Hospital, Pediatric Infectious Diseases.

DR. MOORE: Patrick Moore, the University of Pittsburg.

DR. LYNFIELD: Ruth Lynfield, State Epidemiologist and Medical Director at the Minnesota Department of Health.

DR. SAWYER: Mark Sawyer. I'm a pediatric infectious disease physician, the University of California, San Diego, and Rady Children's Hospital.

DR. HUDGENS: I'm Michael Hudgens, Associate Professor of Biostatistics, the University of North Carolina.

DR. LONG: I'm Sarah Long, Professor of Pediatrics at Drexel University College of Medicine and Chief of Infectious Diseases at Saint Christopher's Hospital for Children in Philadelphia.

DR. GELLIN: I'm Bruce Gellin. I direct the National Vaccine Program Office at the Department of Health and Human Services in Washington.

DR. PIEDRA: Pedro Piedra, pediatric infectious specialist at Baylor College of Medicine, Houston, Texas.

DR. McINNES: Good morning, I'm Pamela McInnes. I'm the Deputy Director of the National Center for Advancing Translational Sciences at the NIH.

DR. BENNINK: Jack Bennink. I'm a researcher at NIAID at NIH.

MR. RAYMOND: Daniel Raymond. I am the Policy Director for the Harm Reduction Coalition in New York.

DR. EDWARDS: I'm Kathy Edwards, Professor of Pediatrics at Vanderbilt University Medical School and an infectious disease specialist at the Monroe Carell Children's Hospital.

DR. STANEK: Scott Stanek, preventive medicine physician, OSD Health Affairs, Force Health Protection and Readiness.

DR. LEVY: Ofer Levy. I'm a pediatric infectious disease specialist at Boston Children's Hospital and Associate Professor at Harvard Medical School. My laboratory study is immune ontogeny, how the immune system changes with age.

DR. WHARTON: I'm Melinda Wharton. I'm the Director of the Immunization Services Division at the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta.

DR. KATZ: Good morning. I'm Jackie Katz. I'm the Acting Deputy Director of the Influenza Division at CDC and also the Director of the WHO Collaborating Center at CDC.

DR. DUBOVSKY: And I'm Filip Dubovsky. I head up clinical development for ID and vaccines for AstraZeneca MedImmune and I am the industry rep today.

CHAIR DAUM: And I'm Robert Daum. I am a pediatric infectious disease guy at the University of Chicago. I work on staff.

So, we have introduced ourselves now and we see that some members are new. Some liaison people are new and they are to be welcomed. The task today is to choose the components of mixtures influenza vaccine. This

is an annual task. It is one we do every year and we will execute our responsibilities starting now.

First, we will have some presentations that will orient us to the topic. I am going to call on Ms. Anissa Cheung. Is she here? Welcome, Ms. Cheung, who will give an introduction. She is the Regulatory Coordinator, Division of Viral Products, Office of Vaccine Research and Review at CBER. Ms. Cheung.

MS. CHEUNG: Thank you. Good morning everyone. So, I am going to introduce the topics for today's VRBPAC meeting.

So, the purpose of today's VRBPAC meeting is to review influenza surveillance and epidemiology data, antigenic characteristic of recent virus isolates, serological responses to current vaccines and also the availability of candidate vaccine strains and reagent.

And after the review and at the end of the discussions, the committee will be asked to make recommendations for the strains of influenza A for both H1N1 and H3N2 and also the B viruses to be included in the 2015 to 2016 influenza vaccines licensed for use in the United States.

So, after the introductions, you will hear several presentations on the types of analysis that are used for all vaccine strain selections that you will be

reviewed. And these presentations include the epidemiology of circulating strains.

CDC will have the presentations on the surveillance data from U.S. and around the world and you will hear some talks also on the antigenic relationships among the contemporary viruses and the candidate vaccine strain. You will hear presentations from CDC, Department of Defense, as well as CBER on these topics. And some methods and techniques that you will hear during the presentations include the hemagglutination inhibition tests, using the post-infection ferret serums, also the hemagglutination tests using panels of serums from humans receiving the recent inactivated influenza vaccines.

You will also hear some data on the virus neutralization test, the antigenic cartography, as well as the phylogenetics analyses of HA and NA of the circulating strain, as well as the candidate vaccine strain. And you will also hear a couple reports on the vaccine effectiveness.

So, there are always some challenges for vaccine strain selections. First of all, the vaccine effectiveness depends on the match between the hemagglutinin of the vaccines and the HA of the circulating strain of the virus. But, because there is a continuous antigenic drift of HA for both the influenza A and the influenza B viruses and the antibodies to HA is really co-related with the vaccine efficacies.

The second challenge is the timelines for influenza vaccine production. They are relatively fixed. So, usually, the strain selection process starts in February and it is necessary in order to ensure the availability of the vaccines for subsequent Northern Hemisphere winter season. In fact, the manufacturers typically begin their productions of one monovalent before the strain selections recommendations. They do it at risk in order to meet the productions time lines.

There are also challenges on the availability of the referenced strain. Which are the candidate's vaccine viruses suitable for vaccine manufacturing? So, the vaccine productions, as you can imagine, depends on the growth properties of strain used for manufacture. They are also strain-specific reagents that are needed for potency determinations, for both the inactivated vaccines and also the recombinant proteins vaccines.

So, I would like to show you how rigid is the seasonal influenza vaccines productions timeframes. As I mentioned before, usually the vaccine strain are being selected at the end of February. There are multiple steps in the vaccine production process, including the generation of the reference viruses, productions of the potency reagents, et cetera, et cetera, and all those steps take around six to seven months before the seasonal influenza vaccines will be available to the public for vaccinations in the subsequent winter season.

Finally, I want to remind the committee that right now we both the trivalent and quadrivalent seasonal vaccines available in the U.S. Actually, they are two antigenically distinct lineages of influenza B that are co-circulating. And they are represented by B/Victoria/2/87 and also B/Yamagata/16/88. And you will hear people referring as B/Victoria lineages or B/Yamagata lineages during the talk.

And at the present time, we have four quadrivalent vaccines are currently licensed in the U.S. And our process for selecting appropriate B strain for inclusion in the trivalent and quadrivalent vaccines is similar to over the years that we used the procedure trivalent vaccine recommendations. First of all, the WHO and also the VRBPAC committees, they reviewed and make recommendations for each formulation for both the trivalent and quadrivalent.

I want to have a quick review of the previous recommendations, which is the 2014-2015 seasonal influenza vaccine strain compositions. So, last year on February 28 we have the VRBPAC meeting, the strain selection meeting, and the committee recommended the following strain for inclusion in the U.S. 2014 to 2015 trivalent influenza vaccines. For the H1N1 strain, the committee recommended A/California/07/2009 H1N1-like virus. There was no change from the 2013 to 2014 vaccine recommendations.

For the H3N2 strain, the committee recommended A/Texas/50/2012 H3N2-like virus. And there was no change from the 2013 to 2014 vaccine recommendations.

For the third component of the trivalent vaccine, the committee recommended B/Massachusetts/2/2012-like virus, which is a B/Yamagata lineages. And there was no change from the 2013 to 2014 vaccine recommendations.

And from manufacturer producing quadrivalent influenza vaccines, the committee recommended a B/Brisbane/60/2008, which is a B/Victoria lineage and this is a second B strain. And this strain has been previously recommended for quadrivalent vaccines in 2013 to 2014.

So, each year in September WHO also recommends influenza vaccine composition for the Southern Hemisphere. So, last year on September 25th, WHO recommended to have two strain change for the influenza vaccine compositions for the Southern Hemisphere, based on the epidemiology data and also the antigenic characterization of the circulating strain isolated from February to September 2014.

So, these are the following viruses WHO recommended to be used for influenza vaccines in the 2015 influenza season Southern Hemisphere winter: an A/California/07/2009 H1N1, pandemic '09-like virus; an

A/Switzerland/9715293/2013 H3N2-like virus; and for the B, a B/Phuket/3073/2013-like virus, which is a B/Yamagata lineage.

WHO also recommended that for quadrivalent vaccines, it recommends for quadrivalent vaccines containing two influenza B viruses containing the above three viruses and also a B/Brisbane/60/2008-9 virus, which is a B/Victoria lineage vaccine virus.

And the two new strains are the H3N2 A/Switzerland and also the B strain, which is the B/Phuket.

So, I want to summarize where we are right now. Okay? Actually, WHO met a little more than a week ago and they have make recommendations for the influenza vaccine compositions for the Northern Hemisphere for the 2015 and 2016. So, the WHO recommended that the following viruses will be used for influenza vaccines in the 2015 to 2016 influenza season for the Northern Hemisphere winter, which is an A/California/07/2009 H1N1 pandemic '09-like virus and also an A/Switzerland/9715293/2013 H3N2-like virus. For the third component for trivalent is a B/Phuket/3073/2013-like virus, which is a B/Yamagata lineage.

It is also recommended for quadrivalent vaccines containing two influenza B viruses containing the above three viruses and also a B/Brisbane/60/2008 live virus, which is a B/Victoria lineages vaccine virus.

WHO also noted, as in previous years, that the national or the regional control authorities, they are responsible to approve the composition and formulations of vaccines used in each countries.

So, now, I would like to pause here and the role of this committee, VRBPAC, to make recommendations of which influenza virus strain should be included for the antigenic composition of the 2015 to 2016 influenza virus vaccines in the U.S. And there are options for strain compositions for 2015 to 2016 trivalent influenza vaccines. For influenza A H1N1 strain, either recommend an A/California/07/2009 H1N1-like virus, which is the current vaccine strain, or recommend an alternative H1N1 candidate vaccine virus.

For the H3N2 influenza A virus, either recommend an A/Switzerland/9715293/2013 H3N2-like virus, or recommend an alternative H3N2 candidate vaccine virus.

For the third component in the trivalent vaccines for the influenza B, you have three choices. First is recommend a B/Phuket/3073/2013-like virus, which is a B/Yamagata lineage, or recommend an alternative candidate vaccine virus from the B/Yamagata lineage, or recommend a candidate vaccine virus from the B/Victoria lineage.

For the second influenza B strain in the quadrivalent influenza vaccines, these are the options. Either recommend inclusion of a B/Brisbane/60/2008-like virus, which is a B/Victoria lineage and also is the

current quadrivalent vaccine recommended strain, or recommend an alternative candidate vaccine virus from the B/Victoria lineage.

So, before I end the introductions, I would like to give a preview for the voting questions for the committee. So, after the review of the data and at the end of the discussions, the committee will be asked to vote and make recommendations for the compositions of the 2015-2016 influenza virus vaccine in the U.S.

So, and more voting instructions will be given at the end of the discussions before the voting. Thank you.

CHAIR DAUM: Thank you very much. We have a moment or two for any clarifying questions on Ms. Cheung's presentation.

Seeing none, in the interest of transparency, Mr. Raymond, can I ask you to introduce yourself again? Because there has been some confusion as to who you are.

MR. RAYMOND: I've been the community representative for the Antiviral Drug Advisory Committee and I was asked to participate in this as the community representative.

CHAIR DAUM: And we welcome you. You are temporary or permanent?

MR. RAYMOND: Temporary.

CHAIR DAUM: Thank you. Okay, our next presentation is from the first of several from the CDC. Dr. Lisa Grohskopf -- I don't know where she is. There she is -- who will talk about the U.S. surveillance. Dr. Grohskopf -- I'm sorry if I messed your name but it has probably happened before -- is the Associate Chief for Policy and Liaison Activities, the epidemiology and prevention branch, the influenza division at CDC.

Welcome Dr. Grohskopf.

DR. GROHSKOPF: Thank you.

CHAIR DAUM: We look forward to your presentation.

DR. GROHSKOPF: Thanks. Okay, good morning. I am going to be giving an update on U.S. influenza surveillance for the 2014-15 season and following that, briefly summarizing --

CHAIR DAUM: Can you stop for one second while we fix the microphones? Sorry.

DR. GROHSKOPF: Sure.

CHAIR DAUM: Try her again.

DR. GROHSKOPF: Hello? Better? Okay.

CHAIR DAUM: Much better. Thank you.

DR. GROHSKOPF: Thank you.

Okay, just to recap, I will be giving a brief update for U.S. influence surveillance for the 2014-15 season and also following that, a brief summary of CDC's early estimates of 2014-15 vaccine effectiveness.

So, first, we are going to cover surveillance. We will start with virologic surveillance. Must of, actually all of the data in the slides that I am going to present come from FluView and FluView is reported weekly from various surveillance systems. The most recent week of reporting is the week ending February 21, 2015.

This slide provides an overview of predominant influenza types and subtypes, as reported to CDC by the National Respiratory and Enteric Virus Surveillance System Laboratories and WHO Collaborating Laboratories located throughout the U.S.

The data here are shown from the 2011-12 season on the far left and the peak on the far right is our current 2014-15 season. The multi-colored bars represent the different types and subtypes of viruses. H3N2 is in red, H1N1 is in orange, yellow is As that have not been subtyped, and green is for Bs. The white line that goes across the graph represents the specimens that were submitted to these laboratories, the proportion that were positive. So, we have

the proportion of positive specimens in white, the colored bars from those positive specimens break down into type and subtype of different viruses.

We can appreciate here that we have, at least as far as the A viruses go, we don't have much orange for the current season. This is an H3N2-predominant season. Compare this with last year, 2013-14, we have, among the A viruses, a predominance at least among the ones that were subtyped, of H1N1 pdm09.

The laboratories that report to the surveillance system differ somewhat in character. Some of them subtype and report A viruses, some do not. This breaks down the same data just including the public health sites, the majority of which do subtype influenza A specimens. So, you can get a better appreciation here because the un-subtyped specimens are out. We have less yellow. We have an overwhelming predominance of H3N2 for '14-'15, as compared with last season, '13-/'14, where the predominance for A was the 2009 H1N1 pdm09.

This represents the remainder of the sites, which by and large do not subtype, so we don't have subtyped As here. You can appreciate that there is predominance of A over B. And you can perhaps appreciate just a little better in this figure that there is a recent and late uptick in the green, the B viruses in most recent weeks.

With regard to antigenic and genetic characterization of viruses, CDC has tested a total of 933 specimens, as of February 21st, since October first. So, October 1, 2014 through February 21, 2015 933 specimens in total, so far. Among these, 27 H1N1 100 percent of which were characterized as A/California/07/2009-like, which is the H1N1 component of that should say the '14-'15 Northern Hemisphere vaccine.

H3N2 of 752 specimens, 30 percent only characterized as A/Texas/50/2012-like, whereas on the other hand, 524 of 752 where nearly 70 percent showed either reduced titers with antiserum produced against A/Texas/50/2012 or belong to a genetic group that typically shows reduced titers.

Among virus with reduced titers to A/Texas/50, most were antigenically similar to A/Switzerland/9715293/2013, which is the H3N2 virus that was selected for the 2015 Southern Hemisphere vaccine.

With regard to Influenza B for Yamagata lineages, 93.5 percent of those tested were characterized as B/Massachusetts/2/2012-like, which is included as the influenza B component for the first B in the trivalent influenza vaccines.

For Victoria lineage, 91 percent were characterized as B/Brisbane/60/2008-like, which is included as the second B component in the '14-'15 Northern Hemisphere vaccine.

For antiviral resistance, among specimens tested by CDC thus far this season, there continues to be, as in previous seasons, among H1N1 pdm09 a low prevalence of resistance to oseltamivir and now also to peramivir, roughly three percent for each of those drugs. No resistance detected in specimens that were tested for zanamivir resistance among the H1N1 pdm09 and no resistance against these three drugs for influenza A H3N2 specimens that were tested for influenza B specimens.

I am going to move on to ILI syndromic surveillance. Again, this is FluView data. The most recent week of reporting, again, is the 21st of February.

This graph summarized data from the U.S. Outpatient Influenza-like Illness Surveillance Network or ILINet for short. To this network, the percent of outpatient visits that were due to ILI are reported weekly from over 2,900 healthcare providers in all 50 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands.

Data are shown here for several selected seasons. The current season is the red line with the triangles and what we see here is that we had a peak of influenza activity, as far as ILI activity reported to this network. In late December early January, the peak percent of visits that were reported to be due to ILI was about six percent. In the current week, we are down to about three percent. That, however, is still above what is considered to be the national baseline, which is the white hash line that goes horizontally across the graph.

The National baseline is calculated from the prevalence of ILI visits during non-influenza weeks. So, we have a substantial decrease from peak but we are still seeing some ILI activity in the U.S.

Another representation of this comes from weekly influenza activity estimates that are reported to CDC from state and territorial epidemiologists. This does not give an indication of disease severity. It really is just a matter of geographic spread and this map appears in FluView every week, starting with the approximate beginning of the season in October.

What we have here is essentially still we are seeing widespread activity and regional activity across a substantial proportion of the country. Widespread influenza activity, which is shown in brown, was reported as of the last reporting week still by 20 states and Guam, with regional activity in orange reported by 25 states, Puerto Rico, and the U.S. Virgin Islands. So, while we are seeing a decline in ILI activity, we still have some substantial influenza activity that is circulating in the United States.

Hospitalization surveillance is next. The next several graphs come from FluSurv-NET which has collected information cumulatively on over 14,000 influenza-related hospitalizations thus far this season.

The first graph is just for this season, 2014-15 and has the data broken down by age group. Each line here represents an age group. The highest line on the graph is the 65 and over age group. What we can see here is

that age group has rather notably higher hospitalization rate thus far this season, cumulatively, than other age groups.

To put this in perspective and see where it compares with previous seasons, the next several graphs look at the individual age groups and break them down by season. So, in this case, instead of each line representing a different age group, each line is representing a different season.

The 2011-12 season is the line at the bottom. This was a relatively mild season, as a lot of folks probably remember. And then we have 2013 in light blue, 2012-13 in the dark blue/dark gray, and 2014-15, our current season, in green. So the top arch in the graph is the current season. This graph represents all ages. We see overall, as of the current, if you compare this season with the same time points in earlier seasons, that is the vertical line you see dropping down from the top curve, we have a higher rate of hospitalizations, cumulatively this season than any of the past three seasons at 51.7 per 100,000.

This examines just 65 and over, as an age group. Again, each line presents a separate season. We have 258 per 100,000 cumulative hospitalizations in this age group and it is very noticeably than the previous three seasons that are represented on the graph.

By contrast, for those 50 through 64 years of age, the light green up top that crosses over the next lower curve is still the current season. At the beginning of the season, somewhat higher than other seasons but we are sort of

approaching something that is on par with the previous two seasons, again, 11, 12, something of an outlier at the bottom.

The 18- through 49-year-olds, similar to the 50 through 64-year-olds, not as substantial a difference in hospitalizations.

The 5- through 17-year-olds, something of a difference with increased rate of hospitalizations relative to the last three seasons but not as marked as those 65 and older.

And finally, the zero through 4-year-olds for whom hospitalization rates thus far are roughly on par with the previous few seasons, again, with the exception of 2011-12.

The last couple of surveillance slides that I have are mortality surveillance. This slide shows the percent of reported deaths due to pneumonia and influenza from the 122 U.S. Cities reporting system, which collects data on cause of death from 122 U.S. cities. The current season is, as in most of these previous graphs, on the far right. As of the most recent reporting week, February 21st, the percent of deaths reported to be due to pneumonia and influenza is declining, since peaking shortly after the beginning of the calendar year but is still above epidemic threshold.

The last surveillance slide, this is a summary of influenza-associated pediatric deaths by week of death reported from the 2011-12 season

to the current season. Death in a child under the age of 18 due to influenza has been a reportable condition since 2004.

To date, CDC has received reports of a total of 92 deaths, of which 83 were associated with influenza A viruses. Not all of these were subtyped but, among the 42 that were, these were H3N2 viruses.

So, just as a summary for the influenza activity portion of the talk, influenza activity in the U.S. began approximately four weeks earlier than average. I should mention also the ILI activity graph that I saw, that activity has been elevated for about 14 consecutive week. The average for the last 13 seasons has been 13 weeks. So, we are on the long end, as far as length of season goes.

Activity peaked in late December, early January, and a moderately severe season.

A drifted strain of the influenza A H3N2 virus predominated. And finally, rate of influenza-associated hospitalizations among persons 65 years of age and older is the highest reported since surveillance began in 2005-2006.

I would like to just briefly acknowledge Lyn Finelli and her team, who do the amazing work in running these surveillance systems, as well as others in the division that contributed to the information in this presentation.

And then, I would like to move on to the -- I can move on to VE or, if the Chair prefers, I can take questions first on surveillance.

CHAIR DAUM: Thank you very much, Dr. Grohskopf. We have a few moments for questions, clarification questions on her presentation. Dr. Long?

DR. LONG: The question is related to your slide about antigenic and genetic characterization. And it may be my naivete but remind us, this is ferret antiserum that is used to --

DR. GROHSKOPF: Yes.

DR. LONG: And it is ferret antiserum raised by, is it vaccination or infection?

DR. GROHSKOPF: Dr. Katz?

DR. KATZ: It's by infection.

DR. LONG: By infection.

DR. GROHSKOPF: Thank you.

DR. LONG: So, the reduced activity -- and I also assume this is hemagglutination inhibition antibody.

DR. GROHSKOPF: Yes.

DR. LONG: This is a summary slide. It is not actually the data.

DR. GROHSKOPF: Correct.

DR. LONG: So, I just want to be sure that I am thinking what you are saying.

So, then the only possibility here is that the virus drifted, that there was somewhat of a mismatch, rather than considering that the vaccine drifted. So, this is evidence of virus drift, circulating virus drift. Is that right?

DR. GROHSKOPF: Yes.

DR. LONG: Thank you. And the drift that you then reported later on or the virus that you reported later on, did it drift during this season or was it drifted when it started four weeks earlier than usual?

DR. GROHSKOPF: I'm not sure I understand the beginning of the question. I think at the time of the Southern Hemisphere WHO meeting there was already evidence of drift in H3N2 viruses, which was the reason for the change in the H3N2 in the Southern Hemisphere vaccine that is going to be given this coming summer for 2014-15 -- 2015, rather.

So, it was anticipated by that point that we might see some drift in our season this season.

CHAIR DAUM: I think Dr. Long is trying to ask when it drifted, if we know.

DR. GROHSKOPF: I think that probably would be better covered by Dr. Katz.

DR. KATZ: Right, and I will be covering that in the next presentation.

CHAIR DAUM: Thank you very much.

DR. GROHSKOPF: Thank you.

CHAIR DAUM: Dr. Levy.

DR. LEVY: Thanks for the presentation. Quick question. It was remarkable seeing the relatively high rate of influenza confirmed hospitalization among the elderly this year, if I understood, higher than prior years. Are there any thoughts about why that would stand out for that particular age group? Do we know the proportion of the different strains that caused those infections in the elderly and whether they were more likely to have strains that were mismatched with a vaccine or it is not clear?

DR. GROHSKOPF: For that particular surveillance system, we don't have information on what influenza virus was associated. We do know that it was an H3N2 predominant season and often H3N2 seasons tend to be

associated, there are always exceptions to anything, of course, but tend to be associated with more severe disease.

We also know that we did have some drift and that we will see in the next slides that I have that vaccine efficacy was somewhat less than we would have liked.

CHAIR DAUM: Dr. Bennink, then Dr. Gellin.

DR. BENNINK: Yes, on this same slide here, in the middle there, you say most were antigenically similar. What does that most mean? Do you have a percentage like you do on the other things?

DR. GROHSKOPF: I don't have a precise percentage for that, no.

CHAIR DAUM: Dr. Katz, do you want to comment on that?

DR. KATZ: I will be covering that in my talk.

CHAIR DAUM: Thank you. Dr. Gellin.

DR. GELLIN: Lisa, thank you. Over 65 is a growing category. Are you able to break down within that the age groups of those over 65 that were hospitalized?

DR. GROHSKOPF: That is a really great question and it is something that in various of our sort of longitudinal studies we are trying to do, for example, within the Flu VE Network, which I am going to cover data for in just

a moment, because over 65 is actually probably a pretty heterogeneous group and it is not something that has been explored very thoroughly.

We don't have a further breakdown, at least I don't have any analyses available for FluSurv-NET, which is the hospitalization data. It has been attempted to do this with Flu VE Network data for vaccine efficacy. But one of the unfortunate things is we tend not to get a very high enrollment of 65 and older in that network. And so we have a relatively low proportion of folks in that network, that age group, to begin with. And then we try to parse those out by age group, we just end up with very, very small numbers that are not really conducive to analyses. There are hopes that there can be increased enrollment in these systems for folks 65 and older over the course of the next few years.

CHAIR DAUM: Dr. Moore.

DR. MOORE: Dr. Katz might be able to address this. We have already partially talked about it but in February of 2014, were there any signs that we could have picked up if we were aware, if we had some global knowledge of influenza, that there was drift in H3N2 and that we could have changed our vaccine recommendations on February 29th or whenever it was we met, based on that?

The second question I would like you to at least try to address as best you can is how long does it take for exhaustion of a strain to occur so that

we no longer have to worry about including a particular strain in a vaccine, once the population is fairly well immune to it.

DR. GROHSKOPF: Just looking at, examining the second question first, I don't really think there are actually data that would indicate when you could take out a strain from a vaccine from a policy perspective. Influenza is variable and different types and subtypes behave differently on a clinical and immunologic basis. So, even if you were to take it out, you would still have the younger proportion of the population coming in. You would still have children that haven't been exposed, for example, to as much flu. So, I am not really sure that there would be any evidence that would point to when we could take something out.

The first question I probably need to refer to Dr. Katz. But if you are speaking as far as in February 29th would have been the VRBPAC meeting last year, there was nothing to suggest anything different at that point, to my knowledge.

CHAIR DAUM: Dr. Katz, the one question?

DR. KATZ: Yes, at the time of late February when the WHO made its recommendation in 2014, there was about one percent of viruses that were showing a low reactivity but this is seen frequently. So, 99 percent of the viruses were similar to the vaccine for H4N2, the Texas/50, which was the recommendation made.

And I will talk about the time line about when the drift virus emerged.

CHAIR DAUM: Dr. Long.

DR. LONG: Dr. Gellin's interested in the elderly. I am interested in the children. So, the mortality that you showed so far 2014-15 in pediatrics is quite remarkable. Do you have viruses from any of those cases? Do you know if they are what they are, if they are H3N2, if they are drifted, and do you know the vaccine status of those children who are pretty vaccinated these days?

DR. GROHSKOPF: Good question. As much as we know, really, at least at this point, about the viruses is what is reported up at the top in the table. We do know that most of them were flu A and among the ones that were subtyped that those were H3N2. I don't have any information yet and don't expect that we will be receiving any about whether they were drifted or not.

With regard to vaccination status, the surveillance team that does examine this data, as they get reports of deaths in, does dig back and try to, as much as possible, determine the number or proportion of children that have been vaccinated and the number of doses that they received.

Generally, we don't really get a complete picture of this until the following months, sometime around early spring, late spring, early summer. Historically, it has been 85 to 90 percent of the children that are reported to this

system have not been vaccinated. That proportion might be slightly higher this year -- sorry -- slightly lower this year with a slightly greater percent of vaccination but they have not yet really ascertained this enough to be comfortable reporting a result.

Generally, the vast majority are unvaccinated, however.

CHAIR DAUM: Our last question is Dr. Levandowski.

DR. LEVANDOWSKI: Actually, it is a follow-up to the discussion about drift and I guess I would probably direct it to Jackie Katz. But often in surveillance, strains are identified that seem to be either dead ends or one-off, so-called. And I wonder if we could get some sort of sense of what percentage of the strains, say in the last year or even now, seem to be of that nature. I bring this up because the question about what to do when a new strain appears and we don't have a lot of information about it.

DR. KATZ: So yes, that is very true, Dr. Levandowski. And if I remember correctly, the sort of very low number of viruses that showed antigenic drift at the time of the February meeting last year, they ended up being of a group that were not the ones that then predominated later through the summer and the fall.

So, again, we would never really make a change based on such a low level of variants. As I said, this happens, there is a constant noise and there

is always dead end drift variance, as you say, emerging. It is when we see an increasing number, a signature antigenic difference and a signature genetic change and the numbers continue to increase that we start working towards considering new vaccine recommendations.

CHAIR DAUM: Thank you, Dr. Katz.

Speaking of Dr. Katz, I would like to thank Dr. Grohskopf for a fine presentation and introduce Dr. Katz as the next speaker.

I said something bad, yes?

DR. GROHSKOPF: Oh, no. If time permits, and you are interested, there is a summary of VE.

CHAIR DAUM: Please continue. I'm so sorry.

(Laughter.)

DR. GROHSKOPF: All right. These next several slides are excerpted from a presentation given by Dr. Brendan Flannery last week and summarized some of the results from the U.S. Flu VE Network that CDC sponsors. And I am going to just give sort of the high level information there.

This is a network of the five sites within the U.S. that are depicted on this list. Also listed we have Alicia Fry and Brendan Flannery, who are the PIs. The U.S. Flu VE Network enrolls patients aged six months and older who

seek medical attention for a respiratory illness. By definition, this illness must include at least cough. It does not have to include fever or feverishness. This analysis presents patients enrolled from November 10, 2014 through January 30, 2015. So, it is not yet a complete analysis, as the season has not ended.

And essentially, cases here among the ill persons that are enrolled, those with respiratory illness are defined as those who have outpatient acute respiratory illness and who are influenza PCR-positive. Controls are those who have outpatient ARI and are influenza PCR-negative.

For the season so far, as of this analysis, there were 4,913 enrolled; 3,281 were PCR-negative; 1,632 were PCR-positive. Among these, 1,537 were influenza A. All of the subtyped influenza A viruses were H3N2. Among these, 764 were genetically characterized by hemagglutinin and HA pyrosequencing; 85 percent were low reactors in genetics groups 3C2a and 3C3a; 15 percent were in vaccine-like groups of 4C.3 and 3C.3b; and then only 6 percent were influenza B viruses.

This is the first results table. This table presents some updated information -- whoops, I'm sorry. This first table presents updated interim VE estimates against any influenza A and B for receipt of one or more doses of any 2014-15 influenza vaccine. So, overall first for all ages in the top line and then broken down by five age categories. Numbers of influenza positive cases and influenza negative controls are shown in the columns. Notably, about 57 percent

of influenza negative patients had received vaccine this season, the highest percentage seen in the flu VA network. Among influenza negative patients, percent vaccinated varied from 41 percent among the 9- through 17-year-olds to 86 percent among those 65 and older.

Adjusted VE for any vaccination across all ages was 19 percent with a 95 percent confidence interval from 7 to 29 percent. None of the age groups specific adjusted VE estimates were significantly different from zero or no effectiveness. And all confidence intervals for age group-specific estimates overlapped, indicating all estimates were similar.

This table updates the early interim VE results from the January 16th MMWR report. Only H3N2 result were shown, since they were similar to VE against any influenza. Adjusted VE against A H3N2 illness was 18 percent, with a 95 percent confidence interval from 6 to 29 percent. Again, none of the age group specific estimates for A H3N2 were statistically significant and all confidence intervals overlapped.

There was evidence of higher VE against influenza B viruses with an adjusted VE against flu B for all patients of all ages of 45 percent, with a 95 percent confidence interval of 14 through 65 percent.

This last results slide, the numbers of genetically characterized H3N2 viruses from patients enrolled in the Network were sufficient to provide an

interim estimate of vaccine effectiveness against the predominant genetic groups of H3N2 viruses as determined by pyrosequencing.

The first row shows the adjusted VE against H3N2 for patients aged six months and older, 114 H3N2 viruses were genetically characterized as vaccine-like groups, 3C.3 or 3C.3b and 39 percent of these patients were vaccinated this season, compared to 57 percent of influenza negative patients. Adjusted VE against H3N2 viruses was 49 percent with a competence interval from 18 through 69 percent for the vaccine-like strains.

The bottom two rows boxed in red with 624 cases due to group 3C.2a and 25 due to group 3C.3a indicates no or low VE against viruses in these antigenically drifted or lower reactor age groups, albeit with wide confidence intervals.

To summarize, we have limited precision of VE estimates for some of our smaller groups, for example, when we break down by age group or break down by virus type, we have smaller samples sizes. And so our precision of our estimate declines and our confidence intervals get bigger. So, that is one important limitation.

Another important limitation is in the interim analysis. We haven't yet adjusted for high-risk conditions, prior vaccination, and things of that nature, and also complete medical records have not yet bene reviewed in order to confirm vaccination status, which, in some cases, is by self-report.

There are insufficient data at the interim to determine full or partial vaccination status of children who are in the age group that might require two doses, as opposed to one. Final estimates may, therefore, differ from our interim estimates.

As always, with an observational study design, also there is the potential for confounding due to differences between LAIV and IIV recipients. This actually refers to data not presented in unvaccinated children and adolescents.

I would like to just acknowledge the Flu VE Network and the team at CDC who put together this data. And I can take questions on this portion, if necessary.

CHAIR DAUM: So, we have a few minutes to entertain clarifying questions on the second part of your presentation. And I want to apologize for not realizing there was a second part.

Dr. Edwards.

DR. EDWARDS: I have two questions. The first is, obviously, the strains that appeared to be drifted do not have good VE. But I also am a little concerned that the VE for the vaccine-like strain was only 49 percent. So, do you have thoughts about that or clarification?

And then I have another question about LAIV.

DR. GROHSKOPF: The VE for the vaccine-like strains in a season with what we would hope for with a good match, generally, we see efficacies around the 60 percent range, sometimes 50. What we will typically see is that will vary across age groups.

One of the difficulties with this particular table is because we have now subdivided H3N2 without B and we are further splitting the groups into vaccine-like, which is not vaccine-like with B, the vaccine-like being the smaller group with only 115, as opposed to the larger group of non-vaccine-like H3N2s, we do end up with a low precision of estimate and fairly wide confidence intervals. So, you see we have six going all the way to 69 percent, which 69 percent would be about on a par with what we might see in the most optimal season.

You know 49 percent is not too far from the 60 percent that we tend to see in a good year.

DR. EDWARDS: So, small numbers.

DR. GROHSKOPF: Small numbers.

DR. EDWARDS: So, one of the benefits of a live attenuated strain has been that there is the thought that it responds better with a drifted strain. So, in your Flu-NET, do you have data about LAIV and whether, indeed, it did perform better than inactivated vaccine?

DR. GROHSKOPF: Good question. For the sake of brevity, I did not include those slides but they were discussed at some length at the ACIP meeting last week.

We did have, in the presentation, an examination of LAIV versus IIV relative efficacy for 4- through 17-year-olds and further broke that group down into the younger 2- through 8- versus 9- through 17-year-olds.

And at least for this sample, for this year, we did not see superior efficacy of LAIV to IVV. Both vaccines had low VE and there was no evidence, at least, again, in this study, that LAIV performed any better.

CHAIR DAUM: Thank you. Dr. Sawyer.

DR. SAWYER: If you could go back one or two slides, I think you showed us two overall summary tables with age breakdowns, only the second of which is in our handout. So, this is the one that I had the question about. I'm not sure I caught the difference between the two tables but on this table, I was struck by the low VE for 18- to 49-year-olds, a population that usually would respond pretty well to vaccine. I am wondering if you have any thoughts about that. And then if you could just explain the difference between this table and the next slide.

DR. GROHSKOPF: This table is all flu and the next is examining A H3N2 and B in isolation. There is not really enough H1N1 this season to really permit any detailed analysis of that.

For the 18- through 49-year-olds, one caveat again I would add is that because this is an interim estimate, in most cases by this point in the year when we do our early estimates, we have not confirmed vaccination status for everyone. It is only by self-report. By the end of summer, everyone's medical records have been reviewed and we know what they have gotten or not gotten.

The other thing is that as part of that medical record review, the high risk conditions and other things that we would normally include in the adjustment for an analysis such as this, I found it included. So, this is still a crude analysis. So, it is possible that once all the things that are normally adjusted for are included, we might see something a little different.

It is also positive, again, this is an observational study and this may just be some kind of fluctuation in what we are seeing with a given age group.

Again, too, with different age groups, we don't know, this is speculation, but if you are in one age group as opposed to another, your previous history of exposure to influenza A viruses will be what it is, based on where you have lived. And it may be that this group just didn't have the same kind of exposure to something. There is no way to know at this point.

What I would probably say is the best answer is that we may have, will likely have numbers that look slightly different when this is all over and

all of the medical records have been reviewed and the final analyses are presented in October.

CHAIR DAUM: Last question, Dr. Long.

DR. LONG: Question. The question of yes/no vaccinated only pertains to this year.

DR. GROHSKOPF: Correct.

DR. LONG: And the question is then related to your inability to show effectiveness if a previous vaccination really protected you or protected you better.

So, the first question is was this a Switzerland in any influenza vaccine campaign in the last five years?

DR. GROHSKOPF: No, it was not.

DR. LONG: Okay. And the mortality in children, do you have data effectiveness against severe influenza, hospitalizations, ICU, mortality, to give us any idea that it performed better there or maybe it performed worse there. We just don't know. These are concerning but we care even more about this severe and fatal.

DR. GROHSKOPF: At present, this network does not collect data and analyze VE against severe outcomes, so deaths or hospitalizations. There

is some discussion about being able to do that, at least for hospitalizations. That is as much as it is unfortunate when we see any, are still a relatively uncommon outcome. So, it may not be possible, at least through this network, to be able to make an adequate assessment but hospitalizations may be possible. I don't know yet if that is something is going to be possible and add it in future years, though.

CHAIR DAUM: Now, I am going to thank Dr. Grohskopf. I hope you don't have more to present.

DR. GROHSKOPF: No.

CHAIR DAUM: And welcome, Dr. Katz, to the committee meeting. Dr. Cox, who has been a fixture at these meetings has retired and Dr. Katz is the Acting Deputy Director of the Influenza Division. You are the Acting Deputy Director --

DR. KATZ: Yes, it is very confusing.

CHAIR DAUM: -- of the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Flu from the CDC.

Welcome, Dr. Katz.

DR. KATZ: Thank you. Well, thank you for the invitation to present the Global Surveillance in Virus Characteristics to this committee today.

What I will be doing is providing a very distilled down version of hundreds and hundreds of pages of data that were reviewed last week at the vaccine consultation meeting in Geneva.

This is complicated data and I am going to need to point.

CHAIR DAUM: We want to be able to hear you.

DR. KATZ: Right, okay. I think he is going to try and give me a mouse, which actually would work better.

Okay, I will just continue for now. So, the data is part of the year-round surveillance that is conducted by the Global Influenza Surveillance and Response System, which is comprised of over 140 National Influenza Centers in 112 countries, six WHO Collaborating Centers, four Essential Regulatory Labs and additional H5 Influence Reference Labs.

So, as you know, the meeting was held last week. It was chaired by Dr. John McCauley, the Director of the WHO Collaborating Center in London. And nine advisors, the Directors of the CCs and the ERLs made the recommendations in the presence of over 26 observers from academia and different reference laboratories, including the veterinary sector because we also review zoonotic influenza viruses.

So, this is just a summary of the countries, areas, and territories that shed viruses during the reporting period. And everything I am going to be

talking to you about today is from viruses that were collected from the beginning of September 2014 through January 2015.

And so you can see that GISR System collects viruses from most parts of the world but there are some notable absences. So, one absence I would just like to mention is India in this reporting period and you may have seen in the last days and weeks that there has been reports from India about some fairly widespread H1N1 pdm09 activity. And so no viruses have been received from India but they are on the way to the GISR System.

This is a summary of the global circulation of influenza viruses over the last year. And if you will focus on the right-hand side, you can see that the numbers of viruses peaked towards the end of 2014 in the last two weeks.

Shown in the various blue or teal colors are the influenza A viruses. So, you can see they predominated with a much smaller proportion of viruses, the orange or salmon colored being the influenza B viruses.

Of the viruses received that were subtyped for influenza A, the H3N2 viruses predominated and there was only modest H1N1 pdm09 activity. And this is shown a little more graphically here. You can see almost three-quarters of the viruses that came in were influenza A. Of those subtyped, 46 percent were H3N2 and only three percent were pandemic H1N1 viruses. A smaller proportion of Bs and the B/Yamagata lineage predominated over the B/Victoria lineage, which you can't even see the piece of pie here.

So, I am going to begin with the characteristics of the H1N1 pdm09 viruses. This is a WHO depiction of the maximum level of activity over this time period worldwide. And you can see that there was really only sporadic and overall low activity with just a few hot spots in a few European countries and then a fairly vigorous late September/October season in Australia.

The numbers of viruses that were detected by the GISR System is shown here. At the end of 2014, this line is in black. So, you can see very low numbers and then just a modest rise showing here in red for the first few weeks of January. But overall, the numbers are very low compared with the 2014, '13-'14 season and other seasons.

So, these are the numbers of H1N1 viruses that have been characterized by the hemagglutination inhibition assay. As you heard earlier, this is the main assay we use for antigenic characterization of influenza viruses. And you can see in green is the period we are talking about at the moment for September through January. And many of the centers, including CDC, this is the China Center, Japan, London, and Melbourne, where only really Melbourne CC had substantial numbers of viruses to test, and others were at fairly low numbers.

This is a phylogenetic tree of the hemagglutinin gene. As you know, the hemagglutinin is the main target of current influenza vaccines. And so, we are very interested to follow the genetic evolution of the HA. For all of the viruses that were characterized during this period, and I am showing here viruses

that are shown in pink, most recent, they are from January 2105. In orange is from December and this is going to be the same for all of the trees I will be showing you. Green and blue are from October and November. So, you can get a sense of how recent these viruses are. They are viruses from Europe, from the U.S., from Asia and Africa, and Canada, and South America and all of these viruses fall into clade 6B, which has been the predominant clade in recent years, with signature changes at 163 and 256 in the hemagglutinin gene.

And it is also shown here the pie chart. You can see the pie chart represents all of the sequence data that is presently available from viruses collected since September worldwide. And so 100 percent of these viruses, although there is only 219 characterized that they are all 6B viruses.

And just for reference, shown in red here, is the California/07/2009 vaccine candidate.

We also look at the neuraminidase gene. We want to make sure in characterizing the viruses that we don't have any unusual reassortment that might appear and that also that the neuraminidase gene is showing a genetic similarity and belonging to the similar clade as the HA. And this is, indeed, the case for the majority of the viruses here.

So, you are going to see a lot of these hemagglutination inhibition tables. They are quite complicated so, I will walk you through this one.

So, what we have here is, so just to back up and remind you, we take advantage of the ability of influenza viruses to bind red blood cells or to hemagglutinate red blood cells. And we can produce reference antigens, viruses, a short panel shown here along the left-hand side, and corresponding antisera raised by infecting ferrets with these viruses and that is shown across the top.

Then, we look at how well the ferret antisera reacts not only with its homologous virus, which is the red titers highlighted but then we also compare these titers, the titers that we obtained with the test antigens, and compare them to the homologous virus. And we are looking for titers that if the virus is antigenically like the reference virus, then we see titers that are within four-fold of this homologous titer. If the virus is not antigenically like the reference virus, then we see a greater reduction, typically about eight-fold or greater.

So, for this pandemic H1N1 table, you can see the reference virus is the California/07/2009. It is grown in eggs. This is the vaccine component and it has a homologous titer with its virus of 1280.

When we look at all the test viruses, and we have viruses here from the U.S., from Canada, South America, and Asia, and one from Africa, you can see that all of these viruses are reacting within two-fold of the homologous titer to the California/07 virus itself, indicating that these viruses are all antigenically similar to the vaccine virus California/07.

If we look at this through antigenic cartography, and this is done for us through Derek Smith and his colleague at the University of Cambridge, and they have become an integral part of collecting data for the vaccine consultation process, they depict the data, the HI data that is sent to them from all of the centers. And this is a combination of HI data from four different collaborating centers, including CDC.

The red dot is the California/07/2009 vaccine virus. And you can see that viruses from 2014, recent viruses which are color coded in yellow, are all tightly clustered around this red dot. And earlier viruses from 2013 also tend to generally cluster around this dot, which indicate that there is no visual evidence of antigenic drift among the pandemic H1N1 viruses.

And just to summarize this in a different way, WHO provides tables which summarize all of the data from the different collaborating centers. And you can see that each collaborating center, although in some cases many of the viruses are small in number, they are larger for the Australian group but all of them are 100 percent like the California/07/2009 vaccine virus.

So, in summary, H1N1 pdm09 activity was generally sporadic in Asia, Africa, the Americas in Europe. There were local to widespread outbreaks in Australia, New Caledonia, New Zealand, in September and October. All of the viruses belonged to the genetic clade 6B and all of the viruses remained antigenically similar to the recommended vaccine virus California/07/2009.

In addition, this Network also conducts neuraminidase inhibitor antiviral sensitivity testing and we report those results as well. So, in summary, the majority of the smaller number of H1N1 viruses that were tested were sensitive to all four neuraminidase inhibitors that are tested. Two viruses did show highly reduced inhibition to oseltamivir and peramivir but remained sensitive to the other two neuraminidase inhibitors and this was likely due to a key substitution at 275 in the neuraminidase, which is known to confer this resistance.

So, moving on to the exciting subtype, H3N2. So, we had very widespread outbreaks in North America throughout Europe, more local or sporadic activity through parts of Asia, South America, Australia, and Africa. But this was, in many countries, a very big H3N2 season. And you can see this from the numbers of viruses that were sent into the GISR System. So, the black line shows the numbers increasing at the end of 2014 and peaking around about the first week of January and with a slow decline now through week five or six. But large numbers compared to previous seasons, even compared to what is shown here in green, which was the 2012-13 season in the U.S., which was a big H3N2 year.

Again, looking at the numbers of viruses characterized by the hemagglutination inhibition assay for the viruses collected during this period, particularly focusing in green. That is the period September through January.

And you can see that over 600 viruses were characterized at CDC, 500 at the China laboratory, but relatively smaller numbers at some of the other collaborating centers and that is due to some of the numbers we had characterizing viruses using the hemagglutination inhibition assay this season. And I will speak more about that in a moment.

So, this is the question, I believe, that was asked earlier by Dr. Moore. To put the drift variant in context, this is roughly the time line of when CDC identified that an antigenic drift variant was emerging. As I indicated earlier, in February, at the time of the VCM and this VRBPAC meeting, a very low proportion of viruses were characterized as low to the Texas/50/2012 vaccine. The HA genes, at that time, belonged to clade 3C.3 and 3C.2, with the 3C.3 viruses predominating at about 80 percent, compared with 20 percent of 3C.2.

And so the recommendation, as you have already heard, was for Texas/50/2012-like virus for the Northern Hemisphere 2014-2015 season.

In March, CDC detected five out of 161 viruses that were antigenically distinct from Texas/50 vaccine virus. And again, this isn't a very large number at all but we decided, since it was a very small cluster of viruses, Dr. Cox, who was still the director at that time, notified immediately the other WHO Collaborating Centers so that they would also look at possible antigenic variants.

In April and May, we started to expand our genetic analysis to identify the signature changes of these antigenic variants and we also began to isolate viruses in eggs, which is required for potential vaccine candidates.

Through the summer, we saw an increasing proportion of antigenic drift viruses. And these are viruses, obviously, flows at a fairly low level, so we weren't testing that many viruses. Nevertheless, we saw an increasing proportion of the antigenic drift variants. And CDC sent two egg-grown viruses to a reassorting lab, in the hopes of making a vaccine and one of these was the Switzerland virus, the Switzerland /971523/2013, which we had received from our London collaborators. And they had received this virus in response to asking the National Influenza Centers have they seen some unusual viruses.

So, in September, as we know, the recommendation was made as we saw an increasing proportion of viruses falling into these drifted variants that would load to the Texas/50 virus.

So, now we are up to date. We are looking at viruses, again, that have come into CDC and to other collaborating centers and national influenza centers. And this is the status of the genetics at this time. And it has gotten a little more complicated to what was happening back one year ago.

So, at the present time, there are multiple genetic groups, the 3C.2 and the 3C.3 clades are still circulating. The drift variants that have

predominated in several countries belong to the 3C.2a group. And I will talk about the signature changes between in these two key groups in a moment. So, just bear with me.

A smaller proportion of viruses belonged to 3C.3a and there was regional differences across the world as to where these viruses were circulating. In the U.S., we saw predominately 3C.2a. In Asia or in China, at least, they saw predominately 3C.3a, just as an example. And so many of these viruses are from China and many of these viruses are from the U.S.

And I do want to acknowledge our DoD colleagues who have kindly provided a large amount of sequence information and that is included in all of our trees. And you can see them as the USAFSAM indicator there. So, this is genetic information that has come from DoD.

So, we still also have 3C.3 viruses and a small group within these referred to as 3C.3b. I'm not going to talk as much about these viruses but you will see in a moment and as Dr. Grohskopf referred to them, these are still in our hands similar to the current Texas/50 vaccine virus, whereas the 2a and the 3a are the drift variants.

Likewise, in the neuraminidase, we see the same clusters, predominantly a 3C.2a group and a 3C.3a group.

This is another way of looking at the data over time. This is, again, from our colleagues at the University of Cambridge in the UK and it shows very nicely, you probably can't see this along here, but the first month is April 2014; the last month is January 2015. So, if you just look at these little bars, you can see how the 3C.2a viruses have really started, have taken off in the last four or five months and predominated. There is still some 3C.3, as I said and less predominance of 3C.3a, which is, of course, represented by the reference virus Switzerland/2013.

And I will also point out I am going to be talking about the 3C.2a virus, Hong Kong/5738/2014. And that falls in here.

So, looking at this a little differently, the global distribution, the pie charts show the sequence information available for all regions of the world and is color coded by the different genetic clades. So, you can see a predominance of orange in North America, Europe, some orange in Oceania; whereas, in parts of Asia, 3C.3a predominated as it did in Africa. Some of these numbers are smaller in some of these other countries. And in South America with very small numbers, actually 3C.3 viruses predominated and Oceania had something of everything.

So, taking a look now at the molecular changes that are signatures for the 3C.3a and 3C.2a groups. So, the 3C.3a virus is represented by the Switzerland/2014 and this is, we generally look at cell-grown because we

know cell-grown viruses are most similar to the viruses that are actually coming out of clinical samples. And once we passage these viruses in eggs, we often pick up egg adaptations. So, we like to compare the cell-grown virus with its egg-grown counterpart, if it is possible, to understand these changes.

So, in 3C.3a viruses, they have signature changes at 138, 128, 159, which you can see, so everything coded in red are the sites where in the globular head where changes are occurring, and 146, 145 and 142. There is also a change at 225, which is in the receptor-binding pocket.

Upon egg adaptation, these viruses acquire three additional changes at 186 and at 219 and these are substitutions that we have seen over recent years commonly occurring following egg adaptation. And they also have a change at 140.

And so this is in reference to comparison to the vaccine Texas/50 virus. If we now look at the 3C.2a viruses, they have some of the same changes at the same -- well, they have changes at the same site. So, at 128, 145, and 159 but for the changes at 159 and 128 there is actually a different amino acid substituted. They also have the receptor-binding pocket change at 225 and a change at 144, which results in the acquisition of a glycosylation site. I'm sorry, it is a loss for glycosylation site.

Importantly, at residue 160, there is an arginine to threonine change that also confers the addition of a glycosylation site in this region. And

this is an important glycosylation site because we see this site sort of being lost upon continued passage either in cells or in eggs.

And this is shown here for the Hong Kong/5738 virus, which is a 3C.2a virus grown in eggs. So, it is has lost the glycosylation site. It also has changes at 194 and it is showing some heterogeneity at the receptor-binding site at 225, as well as a change at 203.

So, before I talk about the antigenic characterization of H3N2 viruses, I want to explain a number of challenges that we have encountered in the last six months or so with these viruses.

So, the neuraminidase of recent H3N2 viruses that are grown in MDCK cells, and that is our typical cell culture system -- when I say cells that is usually the cell culture system we are using. So, the neuraminidase has unexpectedly acquired the ability to agglutinate red blood cells, independent of the HA and that is because of some substitutions at residues 151 or 148. And we found that if we grow the virus in a somewhat different, it is a modified MDCK cell line called SIAT1, then we can reduce the proportion of viruses that had this heterogeneity at these residues and that may be binding through the NA.

But in addition, what we are now doing is we are conducting our hemagglutination inhibition in the presence of a neuraminidase inhibitor. So, we are blocking any effect of the neuraminidase from binding to red blood cells so

that we can be sure that the reactivity we are seeing is through the hemagglutinin antibodies binding to the hemagglutinin.

So, as I mentioned in other challenges that the viruses, the drift viruses in the 3C.2a and 3a groups have a substitution in the receptor-binding site at 225 and we think this may be playing a role in some of the differences in the properties we see. The 2a viruses also have that glycosylation motif that I just mentioned.

And one of our biggest problems is that many of the 3C.2a viruses, when we grow them up, although they have infectious titers, they are no longer effectively agglutinating red blood cells. And so that means a proportion of viruses can't be tested by our traditional hemagglutination inhibition test.

In addition, the motif, as I mentioned, the glycosylation motif which we know is there in the viruses straight out of the human, this motif is lost upon egg-adaptation and we met passage the virus multiple times in cells. So, at CDC, we have been using very low passage of the SIAT cell passage viruses to characterize antigenically by the HI. And we have determined that a majority of these viruses have retained that glycosylation site.

So, in addition to HI, many of the centers were complementing studies by using virus neutralization assays. And at CDC, we were also doing more extensive genetic characterization for more comprehensive surveillance.

So, this is a hemagglutination inhibition table from CDC, where we have used the neuraminidase inhibitor to block the activity of the neuraminidase. As I showed you previously, we have a set of reference antigens and their corresponding ferret antisera along the top, together with a bunch of test antigens, mostly from the U.S. and Mexico.

If you look at the viruses highlighted in yellow on the left-hand side, the other thing I should mention is we have also got the genetic group that these viruses belong to here. So, you can see that viruses from the 3C.3 and 3C.3b groups react well with reference ferret antisera raised to the Texas/50 vaccine virus, indicating that these are still vaccine-like.

But if you look at the lower panel here, the 2a viruses and some 3a viruses, all of these viruses are showing, in general, eight-fold or greater reductions compared to the homologous titers of the Texas 50 virus, indicating that these are now low reactors or drifted from the Texas 50 virus.

I also want to draw your attention to ferret antisera raised against the Switzerland viruses, both an egg and a cell-grown virus and you can see that most of these viruses are reacting within four-fold of the homologous titer for this antisera. And so, the Switzerland antisera is covering well the circulating viruses, whether they are 2a, 3a, and even 3C.3 and 3C.3b.

And similarly, we had a sera raised against a 2a virus, this is a cell-grown virus and it is covering pretty well all of these viruses, also.

This is data from the London group and I really just want to focus your attention on the extreme right-hand side of the panel here. These are two antisera raised to the Hong Kong/5738 virus I mentioned, which is a representative 2a virus either grown in cells or grown in eggs.

And you can see the antisera to the virus grown in cells reacts within four-fold with the majority of viruses tested. But this is not true for the antisera raised to the Hong Kong egg-grown virus, even though it has a very high homologous titer, there is absolutely no reactivity with the test viruses, suggesting that this egg-grown 3C.2a virus is not covering well circulating viruses.

So, a lot of data is condensed into a simple visual representation here. And this is HI data from CDC presented as antigenic cartography. And color-coded here are the different genetic groups. So, you can see the 3C.2, 3C.3 viruses are still in the lower left-hand corner and they are clustering near the Texas/50/2012 representative vaccine viruses.

The 3C.3a viruses are shown in green and they are clustering quite well around the Switzerland cell and egg-grown viruses. The 3C.2a viruses are shown in red. And although they are overlapping fairly quite a bit with the cloud of 3C.2a viruses, that the 2A viruses are generally more diffuse, suggesting that there is antigenic overlap and similarity with the 3C.3a viruses but there is also, in some cases, there is a two- to four-fold difference from the 3C.3a viruses.

In fact, some of this spread in this 3C.2a cloud is due to the low HA titers that we were forced to use in the HI assay.

So, this is, again, CDC data summarizing where the viruses like. So, within four-fold of the homologous titer or low, greater than eight-fold difference, to a number of the reference viruses I have mentioned this morning, viruses grown either in eggs or in cells.

And so for the Texas viruses, you can quickly see the majority of these viruses are falling into the low column. So, the majority of circulating viruses, we have tested over 600, are now low to the Texas vaccine virus, as we have already heard.

If we look at these same viruses to their reactivity to the Switzerland, we see that compared with Switzerland cell-grown virus, 85 percent of them are antigenically similar in a slightly lower proportion but still over 70 percent of the viruses that we have tested are antigenically like Switzerland/2013.

And while we see a similar thing for a cell-grown C3.2a virus, here it is 91 percent. If we look at an example of an egg-grown virus, the Hong Kong/5738 virus, we see that 92 percent are reacting poorly or low to this. So, again, the Hong King virus propagated in eggs as a potential vaccine candidate is not covering circulating viruses.

So, I also mentioned we are doing neutralization assays. And this is data from the London Collaborating Center and it is just to confirm by a neutralization test to show that these are all, these are 3C.3 and 3C.2a viruses, you can see that a ferret antisera raised to the egg-grown Switzerland is covering these viruses well. They are reacting to titers within four-fold of the homologous Switzerland egg-grown virus.

However, if you look at the 3C.2a ferret antisera, if you look at the far right, this is antisera raised to the cell-grown Hong Kong virus. And it does, also, a pretty good job within four-fold reactivity or even better, in most cases, comparable titers to the homologous titer. But if we look at the egg-grown, ferret antisera raised to the egg-grown Hong Kong 3C.2a virus, again, we see large reductions. The majority of viruses are greater or equal to eight-fold down to the homologous virus, indicating, again, that egg-grown Hong Kong virus is not representative of circulating viruses.

And this is just a summary, again, from the WHO data. I think we have said this several different ways but the bottom line if we compare back to the 2014-15 H3N2 vaccine component, the majority, almost three-quarters of the viruses of over 1400 viruses tested at the different centers, the majority is our low reactors and are antigenically drifted from the Texas/50 vaccine.

So, in summary for H3N2, there was generally sporadic activity but regional in the Americas, Asia, and Europe. Viruses belong to the 3C.2 and

3C.3 clades and subclade 3C.2a became predominant in many regions, while the subclade 3C.3a predominated in parts of Asia, Eastern Europe and Africa. And we are still seeing circulation of 3C.3 and 3C.3b.

So, as I mentioned antigenic characterization of H3N2 viruses become technically difficult, in particular, because the predominating 3C.2a viruses have, in many cases, low or undetectable red blood cell-binding activity. And we have used modified HI and virus neutralization to characterize these viruses.

As I just mentioned, the majority of viruses were drifted from the Texas/50/2014-15 vaccine virus. However, most of the viruses were well-inhibited by ferret antisera raised against the cell-propagated 3C.3a virus Switzerland. And although we know that the 2a and 3a viruses are antigenically related, there are some, in some cases, they can be distinguished.

Ferret antisera raised against the egg-propagated Switzerland/2013 virus reacted well with most recently circulating viruses. So, over 70 percent in CDC data.

So, initial data obtained with antisera raised against two egg-propagated 3C.2a viruses showed variable reactivity. And I showed you one example where the activity was very poor and an egg-grown virus was not similar to recently circulating viruses.

So, even though the 3C.2a viruses have predominated, we have limited data to identify an egg-grown potential vaccine virus amongst the 3C.2a viruses.

And just again, the vast majority of viruses were susceptible to all four neuraminidase inhibitors.

So, I am just, hopefully, moving quickly through the influenza B viruses now. There was some widespread activity but, again, it was fairly regional local activity in Australia. Relatively low numbers, as I had mentioned at the beginning of my talk, of B viruses compared to influenza A viruses. And you can see the peak occurring at the end of 2014 and in the red in 2015. Again, low numbers compared to previous seasons.

Where the virus lineage was determined, you can see that the B/Yamagata, shown in blue, if you just look at the far right here, for this season, the B/Yamagata viruses in blue, far predominating over the B/Victoria and this has been the case for the last few influenza seasons.

So, moving to the B/Yamagata lineage, there are currently two clades of B/Yamagata, the clade 2 and the clade 3 viruses. The clade 2 is represented by the current B/Massachusetts/2/2012 vaccine virus for 2014-15. It is a clade 2 virus. And then there are reference B/Phuket/3073/2013 is a clade 3 virus. And you can see in this time lapse, again, for the last ten months, that

over the last five or six months, the clade 3 viruses have far outweighed the clade 2 viruses.

And this is shown in this phylogenetic tree, which has a lot of viruses from Asia, South America, and the U.S., and, again, from our colleagues at USAFSAM. And all of the predominance of viruses are belonging to the clade 3. And you can see this here is the B/Massachusetts/2012 former vaccine component.

And you can see that, I'm sorry there is a bit of overlap with some of these figures here, but 97 percent of all of the viruses for which we have genetic groupings belong to Y3 globally and only three percent are now Y2. And similarly, we see the same thing with the neuraminidase.

So, this is an HI table from London. And if you just look at, again, what is highlighted in yellow, this is looking at viruses reacting with antisera to the B/Massachusetts egg-grown virus. And you can see that there is quite a number of viruses that are now showing eight-fold or greater reduction about at least 50 percent of these viruses in the test. And this is true both for antisera raised to egg or to cell-grown. But if we look at the clade 3 reference virus, B/Phuket, an antisera raised against it, we see that it covers well all of the viruses in this test.

And this is a test from the Melvin Laboratory. And again, they are seeing viruses, these are all from New Zealand and Australia and they are all being well-covered by the B/Phuket/3073 virus.

Shown in antigenic cartography, this is quite a good way to look at the recent viruses colored in gold from 2014 and all of these viruses are now clustering around the B/Phuket reference, either the egg-grown or the cell-grown viruses; whereas, the old viruses from 2013 are clustering closer to the B/Massachusetts, indicating that there has been a drift and a change in genetic clade to the Y3 group.

For the B/Victoria lineage, these relatively small low-level of circulation, so small number of viruses. So, these viruses, again, the hemagglutinin genes, the 1A group is predominating. There is also the 1B genetic group. And the B/Brisbane/60/2008 vaccine virus is a 1A and it is down here at the base of this tree.

And just, again, the pie chart is showing the predominance, 96 percent, of the 1A genetic group. However, in China, they did see some more 1B viruses. So, this is a tree from China and you can see a number of viruses. There is also a couple other viruses from Russia and Australia that are falling into the 1B group but it is a minority worldwide.

Similarly for the neuraminidase, all of the neuraminidase of the B/Victoria lineage are falling into the one 1A group.

If we look at the HI for the B/Victoria viruses, and this is a table from CDC, we are comparing against either the egg-grown or the cell-grown Brisbane/60 vaccine virus and you can see that a majority of viruses are still

covered within four-fold, using antisera raised to the egg-grown vaccine component. However, we were seeing an increasing proportion of four-fold reductions.

Another virus, another reference virus, the Texas/02/2013 virus, which is also a 1A virus and a more contemporary virus, antisera raised to this virus covers well the majority of recent circulating viruses.

And again, through antigenic cartography, you can see that there is overlap and the B/Victoria lineage viruses have not moved on sufficiently from 2013 and 2014 and the cluster is solidly around the Brisbane/60-like or the Texas-like viruses.

And this is the WHO table again. This is a little more complicated because they put both lineages together but if we look at the B/Victoria first and here, the low reactors are shown in red, the majority of centers saw only a low proportion of low reactors to the Brisbane/60/2008. So, a majority, 81 percent, were still being Brisbane-like.

One exception was a small number of viruses characterized by China, where they saw a predominance of low reactors. But there are some HI differences in the methodology of the work conducted at the China lab and they may be contributing to this outlier effect.

For the B/Yamagata, we are referring now to the B/Phuket reference virus, the Y3 virus and 98 percent of the viruses tested reacted well to this Y3 reference virus, which was the vaccine recommendation for the 2015 Southern Hemisphere.

I should say, as Lisa mentioned in her results, the results from the U.S. showed that many of the viruses were still Massachusetts-like. This was not true for other centers and there has been a difference in recent years. Other centers have ferret antisera that discriminate between Y2 and Y3 viruses more acutely. So, in Melbourne and in the London laboratories, the majority of their viruses were reacting low to the B/Massachusetts vaccine virus component.

So, in summary, B activity was low overall. The Yamagata lineage and B/Vic lineage is co-circulated with the B/Yamagata predominating.

For B/Yamagata, the HA genes fell into clades 2 and 3 and the majority of viruses in recent months belonged to clade 3. And recently circulating viruses are well-inhibited by antisera raised against the B/Phuket/3073/2013 virus, which is recommended for the 2015 Southern Hemisphere vaccine.

The B/Victoria viruses, there were a low number tested by most were antigenically and genetically similar to B/Brisbane.

And then, again, the majority of influenza B viruses tested were sensitive to neuraminidase inhibitors.

So, this is the recommendation. And I apologize, there was an old recommendation put in the original package. So, hopefully, you have this single page, which was updated this morning. You have already seen these recommendations from Anissa Cheung from FDA but this was the WHO recommendation made last week for the Northern Hemisphere 2015-16 season. So, A/California/07/2009 stayed the same. The recommendation for H3N2 was changed to A/Switzerland, a 3C.3a virus. And for the B/Yamagata lineage to the B/Phuket/2013.

And for quadrivalent vaccines, the above three, plus a Brisbane/2008-like virus.

So, I will close there and just acknowledge my colleagues from the collaborating centers and from CDC and other contributors to this process. Thank you.

CHAIR DAUM: Thank you, Dr. Katz.

People who are anxious about time might like to know my strategy for kicking us up, and that is to take a slightly shorter lunch break than we are supposed to. I know it is an airplane day. I know we are behind and I think it is essential to have this discussion.

A few clarifying questions, if there are any for Dr. Katz. Dr. Piedra.

DR. PIEDRA: Thank you. There are clear differences from some of the viruses for the antisera raised against egg versus cell-based. My question is, if I understand correctly, eggs are what are used primarily for the World Health Organization Surveillance. Where are the cell-based viruses coming from?

DR. KATZ: Okay, actually most viruses for the WHO Surveillance, most viruses are now cultivated in subculture. And where we can, we isolate some parallel viruses for some key reference viruses. We isolate them in eggs and cells.

The difficulty is we know that growing viruses in eggs, and this is a big problem for H3N2s. It is somewhat of a problem, still a problem for Bs and H1N1s but when we grow the viruses in eggs, we know we can change the antigenic properties. So, we have actually, in the last five, ten years, really switched to the majority of viruses are grown in cells. But we have to use ferret antisera-raised to egg-grown viruses as a comparator because the vaccine virus we need to select needs to be an egg-grown virus. It needs to be a virus exclusively propagated in eggs.

CHAIR DAUM: Thank you. Dr. Lynfield.

DR. LYNFIELD: Thank you, Jackie, that was an amazing presentation. I know that CDC has done a lot of work on the right size influenza surveillance. I am wondering if WHO and the Collaborating Centers have a

similar project. How do you determine that you have gotten enough strains and how is it determined what proportion go on to whole genome sequencing?

DR. KATZ: Right. That's a good question. And I know WHO is also working on a right sizing strategy. As you know, in the U.S. we have a very defined structure for how we receive viruses from the states and we try and be representative. We don't know what the representativeness is, necessarily of some of the other viruses that are collected worldwide but WHO is working towards that effort to make it more representative.

CHAIR DAUM: Dr. Levandowski, then Dr. Moore.

DR. LEVANDOWSKI: I have two questions, one for influenza A and one for influenza B and I will start with the B.

In the B/Victoria strains that you mentioned is B/Texas/02/2013 considered a B/Brisbane/660-like strain?

DR. KATZ: Yes, it is.

DR. LEVANDOWSKI: And is there any information about that strain in terms of how it would perform in eggs and so on? You have that on your slide here but --

DR. KATZ: There is an egg-grown candidate vaccine virus that is available.

DR. LEVANDOWSKI: Okay. All right. And then on influenza A, going back to the H3N2 and the change in the neuraminidase that results in more red cell-binding. Does that mutation have any other functional implications for the viruses, either in terms of say replication in cells or in virulence?

DR. KATZ: Yes, that is a good question and I am not sure I can really answer that. Those studies may have been done but I would -- yes, I really can't answer that question. It's a good question.

CHAIR DAUM: Dr. Moore.

DR. MOORE: There is a GIS program, which is a subgroup of investigators that are measuring efficacy at WHO and I am wondering when could we anticipate that they would have some sort of information on the efficacy of the Switzerland strain that they used in their vaccine, beginning in September. Obviously, there is going to be production lag and so forth but do we have a time frame where we hope to have an answer for that?

And I have a second follow-up question.

DR. KATZ: Yes, so that would be probably coming from the group in Australia. I know that they are still waiting to roll out the vaccine there. One manufacturer, I think there has been a slight delay, but they probably will be beginning studies at least collect serum, maybe not do, of course, full efficacy studies but collecting antisera from individuals vaccinated with the Southern

Hemisphere vaccine. That still is not available but that would be, perhaps a couple of months away. But of course for vaccine effectiveness, you have to wait for the influenza season. So, even the earliest interim results probably wouldn't be available until September, August or September, depending on their season.

DR. MOORE: I have got a second question. I hope this isn't too much inside baseball. The Switzerland strains on the HI that you have a table for the homologous HI titers look like those titers are pretty low, around 320 for their titers, compared to the Texas strains which are all up around 2,560.

DR. KATZ: Yes.

DR. MOORE: So, and while the Switzerland strain appears to have broad reactivity on HI, it doesn't seem like it was very potent in terms of inducing a strong response. Is that a concern for you? What are your thoughts on that in terms of vaccine capability?

DR. KATZ: Right, it is possible. Of course, this is ferret antisera raised in infected ferrets and we don't know how that would translate to humans being vaccinated with, primarily, an activated vaccine.

But there is a constant issue sometimes with normalizing the homologous titers. And in some cases, we just aren't able to elicit very high titers in ferrets.

CHAIR DAUM: Okay, one more question. Dr. Levy.

DR. LEVY: Just a follow-up question on that same conversation. So, obviously, that issue arises every year. And I am wondering what the longitudinal data looks like year to year as to how predictive those ferret titers are in regard to the question preceding.

DR. KATZ: Yes, I don't know that we have really looked at it closely but it is a good point. Again, my point would be that this is infection and it is quite different to an antibody response we would be eliciting through vaccination in a largely primed population. These are all naive animals and that is why we use them because infection of a ferret is almost -- we see a very strain-specific response and that is what we want for this antigenic characterization. So, it might be more akin to how a children, a naive child might react. But it is a good point and we should follow-up and look at that.

CHAIR DAUM: Yes, I think we would like to see the data when you do that.

DR. KATZ: Okay.

CHAIR DAUM: And with that, it is time for a break. I have 10:32. We will reassemble at 10:45 Eastern Time, promptly.

(Whereupon, the above-entitled matter went off the record at 10:33 a.m. and resumed at 10:46 a.m.)

CHAIR DAUM: Our next speaker is Dr. Michael Cooper. Dr. Cooper comes from the DoD. He is the Captain of the PHS and the Leader of the Respiratory Pillar Activities -- maybe he will tell us what those are -- The Division of Global Emerging Infectious Surveillance, the Armed Forces Health Surveillance Center.

Dr. Cooper, welcome, and thank you for doing this.

DR. COOPER: Thank you. And thank you for the invitation.

Again, good morning. My name is Michael Cooper and I am the Pillar Head, as was mentioned just a moment ago, of the Respiratory Disease Surveillance Pillar for the Armed Forces Health Surveillance Center. That is, within the Global Emerging Infection and Surveillance and Response Division. As we are, as you may have guessed, an element of the DoD.

Today, I will be presenting data on the 2014-15 influenza season from our Influenza surveillance Network. Included will be surveillance data from partners within North America, Latin America, Central and East Africa, Egypt, East Asia, and Europe.

In addition, surveillance data will also be presented on our recruit population, which is based at eight different locations throughout the United States.

I will also be presenting four phylogenetic trees that were produced by our partners at the United States Air Force School of Aerospace Medicine, henceforth known as USAFSAM. And I will also be presenting three separate estimates of vaccine effectiveness from our partners at the National Naval Health Research Center, USAFSAM, and at the Armed Forces Health Surveillance Center, the Division of Epidemiology and Analysis.

But since there is some confusion as to who we are and what we do as the emcee alluded to, I want to take a moment or two just to describe and give a background of my organization and our surveillance influenza network.

Again, we are a DoD asset and we are dedicated to the surveillance of infectious diseases primarily but not exclusively in the military community. Our Influenza Surveillance Program extends to over 30 countries with over 400 sites within those countries. In addition to monitoring U.S. military personnel, we have relationships with foreign governments, ministries of health, ministries of agriculture, ministries of defense, and academic institutions, which enable us to do influenza surveillance for select foreign local national populations.

Our laboratories have extensive characterization capabilities, including PCR and viral culture and sequencing abilities as well.

In fiscal year 2014, our network process tested a little over 30,000 influenza or respiratory samples and submitted about 540 samples or sequences to GenBank.

This gives you some idea as to where we are in the world. You can see four continents and, as I mentioned, over 30 countries.

As I mentioned, I wanted to go through some of our surveillance data. I will go through this very quickly. However, I will start off with sort of giving you the lay of the land of our graphs. On the far right-hand side, you will notice that is the most recent flu season, the flu season we are currently in. The far left-hand side, you will last year's flu season. Along the x axis, you have flu week and along the left-hand side, you will see number specimens and on the right-hand side, percent of specimens that are positive.

Again, these data are for military recruits, a particularly interesting population. They are highly vaccinated. Better than 95 percent are vaccinated for influenza and adenovirus. They are at particular risk for respiratory diseases. They are under very stressful conditions. They are living in close quarters. So, looking at these data, give us some idea as to what viruses are evading vaccination. And as you can see, in addition, we are color coded here. H3 is in green. H3 infections are in green, H1 infections are in blue, un-subtyped are red, and influenza B is a slightly darker blue.

But as you can see here, compared to last year, a fairly more intense season, probably related to issues that we have already discussed as far as drift is concerned. And you can see there is two peaks here in December and then one in mid-January. And again, these are individuals, 90 percent of them are between the ages of 18 and 25, so a very young, robust population. These data come from eight centers throughout the United States: South Carolina, Texas, California, very southern states, Illinois. And I can certainly give you more information on that if you are interested.

These data are for active duty personnel and dependent. And by dependents, we mean spouses or children. Again, the setup of the graphs are the same or is the same. You can see that again, it is an H3 season, peaking sometime in December, probably mid-December. Very little in the way of influenza B and a few un-subtyped specimens.

These data come from Europe. We have a substantial number of active duty members and their families stationed throughout Europe and seven countries within Europe, Turkey, United Kingdom, Germany, Spain, and Portugal. So, this gives you some idea as to what we are seeing in our active duty military members and their dependents in Europe.

This presentation was turned in a couple of weeks ago. Since then, I have gotten data and it appears as though week five was the peak of the season, at least thus far.

Latin America, this takes in data from countries in South and Central America, Honduras, Peru, Nicaragua, and Colombia. These data come from local national populations. Obviously, those countries fall within the tropics band. So, you wouldn't expect to see a telltale influenza season and we don't. In fact, from December through January we see very little in the way of influenza activity.

We have a very strong partnership with laboratories in Egypt. These data come from local nationals in Egypt. And again, it is an H3 season. You do see some influenza there.

These data come from Central and East Africa, Uganda, Cameroon, Tanzania, and Kenya. And again, falling within that tropics band, so you wouldn't expect to see your typical flu season.

And these data come from East Asia. This is a mix of active duty military and their dependents and local nationals. We have active duty military in Korea, in Japan, and Guam. But we also have data here from Thailand, Cambodia, and Nepal, and Bhutan as well. Again, that is these data are a mix of really tropical and Northern Hemisphere. But you get some idea as to what we have seen in recent weeks here and throughout the year.

In North America, military members and dependents had experienced moderate to high flu activity, mostly H3. The vast majority, over 90 percent, actually, for H3.

Globally, H3N2 predominated within the DoD Network. And some local national countries indicated substantial influenza B infection.

Now, I would like to share with you some of the phylogenetic analysis put together by USAFSAM. And you will notice Dr. Katz mentioned it that USAFSAM works and actually contributes data to their phylogenetic trees. The data I will be sharing with you today are a subset of the data already shared by Dr. Katz.

I can see 557 total sequences went into developing these trees from 12 different countries, three different continents. I will call your attention to country 1 and country 2. They are countries that are a deployed setting and I can tell you they are in Central Asia. And the rest of the countries are listed there.

Obviously, the H3 is the dominant subtype. And due to the size constraints, a representative tree was constructed from the 523 samples that were H3, using 100 samples. Approximately 73 percent of the H3 viruses belong to the genetic group 3C.2a. My understanding is that was true three weeks ago. Now, it is more like 80 to 82 percent. The remaining belong to 3C.3.

The recommendation from our partners at USAFSAM is to use the A/Switzerland/9715293 for the upcoming flu season. And this is the phylogenetic tree for the H3.

The next slide will be a phylogenetic tree for the H1N1. The hemagglutinin gene of the H1 demonstrates that all the circulating viruses belong to the subgroup 6B, possessing the K163Q and the A256T mutations. Antigenically, the H1 viruses are similar to the current vaccine. And the recommendation is to maintain the A/California/07/2009 for the upcoming flu season.

And this is the phylogenetic tree for the H1N1 virus.

I will share with you now two phylogenetic trees for influenza B. There were a limited number of influenza Bs available for developing these trees. Seventy-five percent of all the influenza B specimen sequences from October to February are the Yamagata lineage.

The hemagglutinin gene for the Yamagata lineage demonstrates that all of the recent viruses belong to the genetic group Y3. Now, I call your attention to the recommendation in red. Since this presentation was put together, some hemagglutinin inhibition data has become available, which has led our partners at USAFSAM to conclude that the Phuket B is more appropriate and for the quadrivalent, the Brisbane virus would be more appropriate for next year's vaccine.

Here you have the Yamagata phylogenetic analysis and the Victoria analysis.

Now, I am going to take you through three separate estimates of vaccine effectiveness, each conducted by USAFSAM, Naval Health Research Center and the Armed Forces Health Surveillance Center. Each uses the case-control study method and logistic regression for adjusted estimates of vaccine effectiveness.

Two of the studies, one at NHRC and the other at USAFSAM, used the control-test negative method and the study carried out by the Armed Forces Health Surveillance at the analysis group used the non-respiratory patients as controls. These are individuals who sought care at about the same time as a control for musculoskeletal ailments or mental health issues but were negative for influenza or had no history or record of influenza infection for that period.

No analyses by flu subtype could be done because the vast majority, over 90 percent of the positive flu samples that we have seen have been H3. And each of these projects confirmed influenza infection by PCR or viral culture.

And these are USAFSAM's findings. The population they looked at was service member dependents. Children, adults, some retirees, very few, but not active duty members.

The analysis was conducted by beneficiary groups, so, looking at overall, then children and adults, and by vaccine type, inactivated vaccine and LAIV.

The models adjusted for age and collection period, also initially adjusted for sex but that variable, due to its lack of impact was left out of the final analysis. There were 468 cases, 694 controls, and 29 percent of cases and 27 percent of controls were vaccinated.

The vaccine estimate for all dependents, all combined, with the inactivated vaccine and estimates for children vaccinated with the inactivated vaccine, were statistically significant and protective.

And this will give you some idea of the age structure of the population we are dealing with here. You can see the vast majority are under the age of 36. So, it is a very young population.

And here are the vaccine effectiveness estimates. As you can see, children vaccinated with the inactivated vaccine, there was a 48 percent VE associated with it. That appears to drive the overall estimate, which is 40 percent for the inactivated vaccine but we see no statistically significant vaccine effectiveness for the LAIV in this population.

The next analysis I will share with you was done with our partners at Naval Health Research Center, located in San Diego. The population that

they used in their analysis were civilians only. These were dependents of military members who reside either in Southern California or in Illinois or civilians at an outpatient clinic near the US-Mexico border.

These analyses adjusted for age, study population, military versus nonmilitary, and also initially, again, controlled for sex but was left out of the final analysis due to lack of impact.

There were 140 cases confirmed by PCR or viral culture and 278 controls. These are test-negative controls. Ninety-five percent of these individuals -- of the cases were positive for H3N2. So, no analysis could be done by different subtype of influenza.

The vaccination rates were 17 percent for cases and 37 percent for controls. And the adjusted vaccine effectiveness for H3 was 47 percent and that was statistically significant.

And this gives you some idea of the age structure of the population studied here. Again, fairly young. The vast majority are below the age of 18.

Again, they attempted to look at vaccine effectiveness by age group, children versus adults. Because of the small numbers, though, neither were statistically significant of their own, on their own. So, overall, the

inactivated vaccine had a vaccine effectiveness of 53 percent. And again, that was statistically significant.

Couldn't look at LAIV. Very small number of their cases and controls, somewhere in the neighborhood of 25 to 30 reported vaccination with LAIV. So, no analysis could be done by vaccine subtype.

The last analysis I will share with you today was done by the Armed Forces Health Surveillance Center Epi and Analysis Group. This population was active duty members only. That is including individuals from Army, navy, Air Force, Marines, and Coast Guard. These are both within the United States and assigned outside of the United States.

There were 2,045 cases; 8,015 controls. Basically what was used here was a health control, rather than a test-negative control. And these are individuals, as I mentioned earlier, who had sought some care for something unrelated to influenza and had no record of influenza infection for the current time period.

These cases and controls were matched by age, sex, date of encounter and location of encounter. The model is adjusted for a five-year vaccination status. That is, if an individual had any record of vaccination in the previous five years, they were marked as a yes. If not, then no.

Overall, vaccine and vaccine-type -- overall, vaccine-type and VE were calculated.

Eighty-nine percent of cases and eighty-eight percent of controls were vaccinated. So, you have a highly vaccinated population here. And remember, these are active duty members only. So, the vast majority will be between the ages of 18 and 35.

Ninety-two percent of cases had prior flu vaccine in the previous five years. Not surprising. It is policy for active duty members to be vaccinated every year.

Adjusted vaccine effectiveness of negative four for those who received the inactivated vaccine. That was not statistically significant. And the adjusted vaccine effectiveness of negative 32 for those who received the LAIV vaccine, this was statistically significant. These beg the question about timing of vaccine, potential of waning immunity. We have individuals who are getting vaccinated as early as September in the military. So, many questions need to be answered.

This is your age structure for this population. Again, the vast majority are below the age of 40. So, I cannot answer questions about the aged population. And in this particular situation, I can't tell you much about those under the age of 18 either.

Here is your vaccine effectiveness estimate, the overall, and broken down by flu subtype and vaccine type. And as you can see, the LAIV, when broken down, just looking at A is statistically significant and negative in the wrong direction.

Summary results. For civilians, vaccine effectiveness was statistically significant for the inactivated vaccine. As I said, for civilians and for children in the USAFSAM analyses. These analyses indicate that the inactivated vaccine prevented between 40 and 53 percent of medically-attended influenza cases.

For military members, vaccine effectiveness was not protective and estimates for LAIV even indicated an increased risk for infection. We believe this is likely due to unmeasured confounders or possibly chance. We do not believe that LAIV increases the risk of influenza infection.

Again, as I mentioned earlier, questions as to vaccination timing and also history of vaccination, whether or not that impacts antigenic response to an imminent vaccination.

Limitations, subjects were sick enough that they sought medical attention. So, we can't really comment on vaccine impact for less severe cases. The active duty military population is highly immunized, as I mentioned before. This could have a negative impact on vaccine effectiveness, potential methodological issues because of the lack of a good comparison group or

biological effects, such as attenuated immune response with repeated exposures.

The military population is younger and healthier. So, we can't really comment on the vaccine impact in older, high-risk populations and we were unable to compare flu subtypes because the vast majority were age three.

Some of our vaccination data relied on patient recall. And that is certainly a limitation but it was, actually, fairly rare.

I would like to acknowledge our partners throughout the world, too many to go through by name but we do appreciate their work, especially NHRC and USAFSAM.

I'm happy to take any questions.

CHAIR DAUM: Thank you very much, Dr. Cooper. Some food for thought and a tour de force.

We have a few minutes for questions and let's see what is on people's minds. We have some time this afternoon to explore issues that you have raised but these are clarifying questions. Dr. Edwards.

DR. EDWARDS: Okay. Do you have any systematic assessment of immune responses to the vaccine in your population? I mean, do you have a cadre of people that you look at every year or that you follow in terms of people

that are previously vaccinated or look at cell-mediated responses or those sorts of things? Are there any of those studies that WRAIR conducted within your group?

DR. COOPER: There is nothing ongoing at this point. There is one proposal that DIS is potentially going to fund from WRAIR that would look at these questions.

Since we have a serum repository with about 60 million samples, every U.S. military member will give a sample every two years. So, there is potential for this kind of work with that repository.

CHAIR DAUM: Dr. Piedra.

DR. PIEDRA: Yes, thank you very much. For the control test-negative studies, what was the definition used for looking at vaccine effectiveness? So, for the U.S. Influenza Effectiveness Network, it is acute respiratory illness or relatively broad.

DR. COOPER: The first backup slide would be -- I'm getting to it, I swear. It will just take a little bit. We are back to my disclaimer now. It is the last slide. Just let me take it through and I will get it there. Thanks. My backup slides are not here.

All right, we have a patient definition and I think it might answer your question. Basically, fever, a sore throat, cough, is part of the patient definition and that also was used in the --

DR. PIEDRA: So, it was more consistent with influenza-like illness, rather than just an acute respiratory illness.

DR. COOPER: Yes, I think that is fair to say. And do we have any -- there you go.

DR. PIEDRA: Thank you very much.

CHAIR DAUM: Dr. McInnes to the rescue.

DR. COOPER: Are all backup slides gone? Okay, any other questions?

CHAIR DAUM: Yes, Dr. Levy is next.

DR. LEVY: It seemed like you had what may be an outlier result with a live attenuated vaccine, which you mentioned. Do you know if in prior years you have observed anything like that? Maybe not an enhanced disease but just a less positive effect.

DR. COOPER: Last year we looked at LAIV and found no statistical vaccine effectiveness but my understanding is that wasn't uncommon.

A year prior to that, we found vaccine effectiveness, moderate vaccine effectiveness for both the inactivated and the live attenuated. Like I said, moderate, though, in the 40 percent range.

CHAIR DAUM: Dr. Long, last question.

DR. LONG: One of the confounders that I am sure you have thought about seems potentially quite significant. And that is in a case control, you have to assume that the groups you are looking at differ only in their vaccination and their exposures the same. But it looks like your controls derived mainly for influenza was in your backup slides before influenza was really a factor. So, they were not as likely to be exposed.

And also, they clustered in the group under five, which is school-aged children who are, mainly, equally exposed.

DR. COOPER: Yes, I think that is a very good point.

CHAIR DAUM: Dr. Cooper, thank you so much.

DR. COOPER: Sure thing. Thank you.

CHAIR DAUM: The next two presentations are from FDA folks. We have Dr. Ye coming up. He is the Senior Investigator of the Division of Viral Products, Office of Vaccines Research and Review at CBER. Dr. Ye, welcome.

DR. YE: We don't know how to deal with high tech.

CHAIR DAUM: We have a temporary computer-related glitch, we are about to fix, I hope.

DR. YE: Okay, I think it is when we load my slide I don't want to waste people's time just to start to talk on something.

What I am going to be talking about is if you have my handout, you can look at that. I just realized that because I use the same template for year by year, I never bothered to look for the title. And I note is my title a little bit misleading. I am not going to be talking about the human response to the vaccine strain. Rather, we are going to compare the relative HI Titers over circulating virus with those of vaccine strain. What we want to look at is that see how well the circulating virus reacts to the antibody stimulated by the vaccine and see the relative antibody, whether that one reacts well or reacts poorly, compared to the vaccine strain.

The problem for human serology study, unlike the ferret study, you have homologous serums for this case, such as Switzerland. For humans, we don't have this luxury. We don't have a vaccine. So, what do we look at to compare the one-way immune response over the circulating virus with a vaccine strain?

I don't know if you want me to talk without a slide or just -- okay, I think it is okay.

CHAIR DAUM: Dr. Ye, we think we can fix the problem within five minutes.

DR. YE: Okay.

CHAIR DAUM: Do you want to wait, take a break for five minutes or do you want to keep talking?

DR. YE: I don't know. If I talk more, I probably will make some mistakes. But anyway, I think I can keep talking if it is not candid talk but it just gives them my thought, too.

And as I said, you only look at the comparison of the antibody. So, the flu HI titers or GMT doesn't mean anything in this study.

So, this is why the serum from clinical trials immunized at least the current trivalent vaccine or quadrivalent vaccine. And then to increase the sensitivity of the study, the serum was usually pre-screened to choose the positive antibody against either one or three or four components.

So, the study usually, we used to use HI assay. That is our primary method for this study. And Dr. Katz mentioned that is for some virus, especially the H3N2 virus, there is a problem with the hemagglutination to the red blood cells. So, in some studies, we used macro-neut assay to confirm HI assay or HI assay wouldn't give you a clear answer.

So, the serum usually come from different country. For this case, it would come from Australia, from China, from Japan, or from U.S. So, as I said, the serum are from clinical trial, from quadrivalent or from trivalent. Then, the serum are distributed to at least six labs to do a study.

And then what I am going to present to you is a summary of the all six labs, even the viruses that we choose, the current circulating virus that we choose for our study, not all of them was tested by all labs.

Usually because I said that is a comparison, so you have to have the vaccine virus as a comparator and then we choose the representative virus to see the immune response.

And then of course it is because of the problem of the egg adaptation, usually the virus for same virus, if we can, we choose two pairs, either eggs with egg or with cell, and see how that one reacted to the serum immunized with a current trivalent or quadrivalent vaccines.

Okay, I think it is okay. Okay, so, if you have my handout, on slide number seven, that is the summary of the relatively geometric mean titer of the circulating virus compared with the reference virus, which is California H1N1.

On the far left column are the relative GMT titer to the reference virus which is H1N1 egg propagated virus. And the blue column shows the

reactivity to the adults. Then the red one or brown one is the reactivity to the adults. Then, the blue one is children.

Because we use this virus as competitor, so we set that one as 100 percent. Whatever circulating virus compare with this virus. So, you can see the rest of the virus are boxes with the black. So, that is the other circulating egg or cell viruses.

CHAIR DAUM: Excuse me one minute. Dr. Levy, you look perplexed.

DR. LEVY: Are we looking at slide seven?

CHAIR DAUM: Can you use your microphone, please?

DR. YE: Yes. The question is are we looking for slide seven.

DR. LEVY: So, in slide seven, I think the adults are in blue, aren't they?

DR. YE: Yes, adults is blue.

DR. LEVY: Okay, I thought you said something different about the colors. I didn't want to make a trivial point but I also don't want us to be looking at different things while you are talking about something else. So, sorry for the interruption. I just wanted to make sure we are on the same page.

DR. YE: Okay, I think we got this way talk without slides. In that case, we communicated pretty well.

CHAIR DAUM: Okay, I hate to do this and I apologize in advance for it but we are going to take a five-minute break in our seats. We are not going to get up. We are not going to walk around but we are going to take a break while the FDA fixes this problem.

(Whereupon, the above-entitled matter went off the record at 11:24 a.m. and resumed at 11:27 a.m.)

CHAIR DAUM: Okay, we're going to resume the meeting now. Sorry about the delay. And, Dr. Ye, you have your slides?

DR. YE: Yes, I do.

CHAIR DAUM: Please continue.

DR. YE: I am going to continue. Okay.

CHAIR DAUM: Would everybody please be quiet?

DR. YE: Okay, now we are on the slide where it is just talking about it. And here you can see that. This is the GMT titer to the reference bars. And of course, that we sit at 100 percent when they compare with circulating virus.

And you can see here is the either egg isolates or the cell isolates in that black box. And what you are going to see is see the relative GMT titer compared to the reference bars because we don't have lines that reach how low will be low, how high will be high. It is just relative.

And as you can see, the majority of this circulating virus, either egg or cell, react reasonably well with compared with the vaccine virus.

And the last column is the summary is the average over all the virus. As you can see here, we can say that the circulating virus react reasonably well to the vaccine strength. So, in that case, we can say that the vaccine strain, the virus that contains current H1N1 stimulated antibody covered reasonably well to the circulating virus.

And then in conclusion to that, if you use this virus for the vaccine, it should be okay to cover the circulating virus. If the circulating virus comes back one year later or not, because when you look at it as it is now and one year later, we don't know what kind of a virus is going to come out. But we do the best we can. So, from this we can say, the current virus covered well by the current vaccine composition for H1N1.

Okay, as I said, the vaccine containing California H1N1 stimulate anti-HA antibodies of the similar GMT titer to the vaccine strain and the most, a majority of circulating virus.

Now, we go on to H3N2 and this is the difficult one. As. Dr. Katz mentioned that there is some drift and mutation of egg isolated virus when the cell isolated virus are passing in eggs. So, in this study, we include the reference virus from Texas/50 egg or cell just as a comparator. I didn't mention that for one of the manufacturer from Japan they use New York/39, rather than Texas/50 for H3N2 components. So, in this study, we include that one as compared to.

And then the following ones are the representative current viruses. As you can see here, we include a pair of the egg or cells. In this case, you can see that it is a Switzerland virus. And the blue one are the 3C.3a clade and the green ones are the 3C.2a clade. So, we wanted to see how the current Texas-like virus covered well or not well to the circulating virus.

Okay, similar figures for the H1N1 and here, I want to go through again. And in this particular figure, where the comparator is egg-derived or propagated Texas/50 virus and compare that one with the circulating virus. And here for your convenience, I boxed the 3C.3a is black box and the 3C.2a with the red box.

As you can see here, the majority of all of those virus react poorly to the Texas/50 egg isolates. And the last few columns, you just try to break them down to the all H3N2 or cell-propagated circulating virus or egg-propagated virus or even 3C.2a or 3C.3a. But you can see overall whatever you measured, they all reacted poorly to the vaccine strain.

Now, if we compare if the comparator is a cell isolate, as you can see here, the reason is that the cell-isolated virus usually, in most cases, stimulate a relatively low homologous HI titers. So, when you compare with the circulating virus that you can see that circulating virus have a relatively higher titer compared with the egg ones. But overall, you can see here the majority of 3C.2a or 3C.3a reacted poorly, even to the cell-propagated viruses.

And then similar, you can see the breaking down of those viruses reacted poorly to the H3N2 Texas-like viruses. So, that it indicated the current virus is stimulated anti-serum it has not reacted well to the most of the circulating virus and indicated that this needed to be changed.

Okay, here is the summary of these slides. The vaccine contains A/Texas/50 antigens that stimulate anti-HA antibody of low GMT Titer of the circulating viruses including 3C.3a and 3C.2a as compared to the referenced viruses.

Now we go to the B serology studies. Again here, it is because B contained two components. The one is the Yamagata one, represented by the B/Massachusetts and Victoria, represented by B/Brisbane. And then the representative viruses we group as the Yamagata lineage or the Victoria lineage.

Now, this slide shows the antibody response to the B/Yamagata components. Again, here is comparator and then you see the rest of the viruses.

What I box is that the black one represents Yamagata isolates and the red one are Victoria-like virus.

As you can see, this is not dramatically lower but it is a relatively compared with the vaccine strain, which is Massachusetts and most of the virus have a relatively low GMT titer when compared with the Massachusetts virus.

Because we don't have a lot of cell isolators for the B/Victoria and then, in this study, shows that HI antibody response to the B/Victoria of quadrivalent because of our quadrivalent vaccine contained the B/Brisbane. So, we used the B/Brisbane as a comparator in this study. As you can see here, this is the antibody relative GMT titer to the Brisbane viruses and the Texas cell or Texas egg was compared to. And you can see here that the representative B/Brisbane-like virus has reacted quite well, when compared with the vaccine strain.

So, as I said here, is the vaccine contains the Massachusetts the antigen elicited anti-HA antibody of lower GMT titer of the circulating virus when compared with the vaccine strain. And as you expected of that, I think it does not contain the antigen to the other viruses. So, the Victoria they need is lower as well.

However, when the vaccine contains both the Yamagata and the Victoria lineage, of course, for the Yamagata circulating virus did not react well to

the Massachusetts. However, the vaccine reacted pretty well to the circulating virus of the B/Victoria viruses.

And here is our summary. The vaccine contained H1N1 antigen stimulated anti-HA antibodies of a similar GMT titer to the vaccine reference virus and the majority of representative H1N1 pdm09 viruses for H3N2 vaccine contained A/Texas/50 antigens induced anti-HA antibody of a lower GMT titers to the majority of representative H3N2 viruses, when compared with the vaccine strain.

And for the B viruses, the vaccine contained B/Massachusetts antigen stimulated anti-HA antibody of lower GMT titers to the majority of the circulating Yamagata lineage and Victoria lineage viruses when they compare with the vaccine reference viruses.

And then the vaccine contained B/Massachusetts as well as the B/Brisbane antigens stimulate anti-HI antibody of a similar GMT titers to the Victoria vaccine. So, that is indicated to have extra antigens they will be better for the coverage. Thank you.

CHAIR DAUM: Thank you, Dr. Ye. And given that we are now seriously behind, we will take one or two questions only, if there are any. Dr. Moore?

DR. MOORE: Dr. Ye, I am a little concerned in this meeting that the overall reliance on HI testing for all these strains, since it is only measuring one antigen and not even neutralizing antigen per se. So, is there an attempt by FDA to move towards other testing that would give us a better indication of vaccine efficacy or a better predictor of vaccine efficacy?

And secondly, have you measured neuraminidase levels within any of these strains, since there is variability, even within the vaccine seed stocks of a component and at least has some broad neutralization, or at least some broad antigenic capacity.

DR. YE: Okay, I think, sir, you have two questions in here. One is what kind of methods were used in the study. Because we don't have slide, I didn't mention for some subset of the study, we used micro neutralization in this study. Because micro neutralization assay utilized a lot of serum, technically, very hard for us to use that method for this study. This is number one answer your question.

And number two, I think you related this one to the efficacy. As I mentioned in the beginning, we are not looking for the immune response of the circulating virus -- I mean the vaccine strain to the human population because that probably related it to the efficacy. Because in this study, what we wanted to compare, the relative anti-HI antibody of a circulating virus that we use the

vaccine strain. So, that is the serum has been manipulated by exclude low titer. So, the flu titer in here doesn't mean anything.

So, I think for this study, the limitation is to see the relative antibody titer or the circulating virus with the vaccine to see whether those vaccines do cover well or poorly to the circulating viruses. We are not answering any questions about efficacy.

CHAIR DAUM: Thank you, Dr. Ye. One more question, if it is available. If not, move on. Okay, thank you, Dr. Ye.

Our next speaker is Dr. Manju Joshi. She is a lead biologist of the Division of Biological Science Standards and Quality of the Control Office of Compliance and Biologics Quality of CBER FDA. She will speak on candidate vaccine strains and potency reagents. Welcome, Dr. Joshi.

DR. JOSHI: Good morning. I am Manju Joshi and I work in Division of Biological Standards and Quality Control in the Office of Compliance and Biological Quality at CBER.

Division of Biological Standards and Quality Control, we call it DBSQC because the name is too long, in collaboration with other essential regulatory laboratories from UK, Japan, and Australia participates in generation and calibration of reagents acquired for testing of influenza vaccine. Our Division

also manages and provides these reagents to all the U.S. licensed manufacturers.

In the next 15 minutes or so, 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 2015-2016 season.

So, for influenza A H1N1 type, the current vaccine strain was A/California/07/2009 H1N1 pandemic09-like virus. A number of reassortants have been used in the manufacture of vaccine last season. These include reassortant X-179A and X-181 for A/California/07 and a reassortant named as NIB-74 for A/ChristChurch/16/2010, which is another A/California-like virus. A/Brisbane/10/2010, which is another A/California-like virus was also used in some of the vaccines. Most of us in this audience know that WHO has recommended that there be no change for H1N1 strain for upcoming influenza season.

We all understand that the inclusion of WHO proposed strains in the vaccine is based on the approval of the committee today. For now, let's look at some of the reagents that are available for testing this strain.

Last season, homologous reference antigen two lots were prepared by CBER and were provided for X-179A reassortant and similarly, a lot of reference antigen designated here was prepared for X-181 and was made available.

In addition, some manufacturers had used reference antigen from other essential regulatory laboratories such as egg-derived antigen for X-181 from TGA in Australia, NIB-74 from NIBSC in the UK, and similarly, a third cell-derived reference antigen for A/Brisbane/10 from NIBSC was used by manufacturers.

There is lots of antibodies were prepared by CBER and are listed up here.

I would like to point out that CBER will authorize the use of these reagents from other ERLs on a case-by-case basis. And this is more for the manufacturers, not so much for the committee, and users of the reagent that DBSQC would like to know ahead of time which reagents each of the manufacturers will be using. This will help us in planning for a lot of these activities which we perform at CBER.

Coming to the H3N2 strain in the vaccine, for 2014-15 season, the recommended strain was A/Texas/50-like virus. And two reassortant, the X-223 and 223 A were developed and used in vaccine. WHO has recommended a change of this strain and for 2015-16 influenza season, A/Switzerland/9715293/2013 H3N2-like virus has been proposed. The various candidate virus in this group include A/Switzerland and A/South Australia/55/2014, A/Norway/466/2014 and A/Stockholm/5/2014 virus.

CBER plans to generate all authorized homologous reagents, if this strain is selected by the committee.

I would like to point out that we, at CBER are committed to meet these reagent needs and expect that the reagents will be available by June 2015.

And again, I would like to emphasize that we have put the target date as June 2015 but still, every effort will be made by us to try to provide reagents earlier.

We will regularly update the industry with the our reagent preparation progress in the WHO IFBMA bi-weekly teleconferences, which always follow after the strain announcement.

At this point, I want to point out that this strain was also recommended for influenza vaccine for Southern Hemisphere and because of that, the reagents for IVR175, reassortant of A/South Australia are currently available from TGA. Similarly, reagents for NIB-88 of A/Switzerland are currently available from NIBSC UK.

I want to reiterate that CBER will authorize use of these reagents from the ERLs on case by case basis.

Coming to the influenza B strain for a trivalent vaccine for 2014-15 season for a trivalent vaccine, B/Massachusetts/2/2012-like virus from the Yamagata lineage was recommended as a B strain.

Last season, Wild Type B/Massachusetts and reassortment 51B were used in the vaccine. The reagents for both of these were made available by all the essential regulatory laboratories.

This year WHO has proposed a change in the strain. For 2015-16 influenza season, WHO recommends that the trivalent vaccine contain a B/Phuket/3073/2013-like virus from B/Yamagata lineage as the B component. The candidate virus for this group include the Wild Type B/Phuket and a B/Brisbane/9/2014 virus.

If this strain is selected by the committee today, CBER plans to either generate or authorize the use of the reagents from other ERLs. The target availability of date for the new reagent which we will prepare, the B, again, June 2015.

Again, I want to bring, by now, everybody is known that this strain was recommended for Southern Hemisphere as well and B/Phuket and B/Brisbane/9 reagents have been made and not available from NIBSC. Similarly, the reagents for B/Phuket were also available from TGA.

One more time, whenever we talk of reagents, we have to bring up the point that it is important to consult DBSQC prior to use of the reagents and CBER will authorize the use of reagents from other ERLs on a case by case basis.

As we all know, quadrivalent vaccines are supposed to contain three strains that are recommended for the trivalent vaccine with an additional B strain from alternate B lineage referred to second B strain.

During the 2014-15 season, WHO had recommended that the second B strain for a quadrivalent vaccine B/Brisbane/60/2008-like virus from B/Victoria lineage. A number of candidate viruses were made available and of those, B/Brisbane/60 was used in the vaccine.

WHO has recommended no change from 2014-15 season and B/Brisbane/60/2008-like virus is recommended as the second B strain with our various candidate viruses from this group available.

I would just like to point out that since B/Brisbane/60 was the second B strains, CBER had prepared and had authorized reagents for second B strain, which included a reference antigen for an egg-derived B/Brisbane/60. There are multiple lots available, three lots, basically, from CBER for this. And at this point, I would like to emphasize that for testing of the two B strains in a quadrivalent vaccine, use of a mixture of reference antigen for testing the B strain is recommended.

Usually testing the B strain in a quadrivalent poses challenges. And this is based on our experience that few limited strains and also work done by others tells us that the mixture of reference antigens for two B strains seems to be suitable for potency testing. The same approach will be evaluated with introduction of new B strains this season. And the thought about using a correction factor with the use of a specific reference antigen are not recommended.

I just wanted to add that in the past, CBER had authorized the use of B/Brisbane/60 antibody reagents from NIBSC and TGA, especially for some of the quadrivalent testing.

So, lastly, I would like to make some comments about production and use of SRID reagents. The selection of multiple strain and reassortants, along with production of vaccine in different platforms pose challenges to preparation of reagents and timely supply of the reagents. But every year, we try our best and put every effort to make sure that right reagents are available in a timely manner for potency testing of vaccine.

CBER-authorized reagents should be used to test potency of vaccine marketed in the U.S. Homologous reference antigen is the most optimal and efforts are made to prepare such reference antigen as required for testing with different vaccines.

If a heterologous reagent needs to be used, the performance of such reagent will be verified and authorized by CBER. And if other options are not feasible, CBER may recalibrate a heterologous reference antigen.

And lastly, this is again more for the users of the reagent, is the use of reference antigen and reference antiserum as a calibrated pair from same ERL source is desirable to avoid discrepancy.

So, lastly, just some few of the reminders I would like to make, which I do every year at this forum and again this is nothing to do with -- is now no interest to the committee, per se, but this is to the audience who are from the manufacturer side and users of the reagent that please, we request that you communicate to CBER your plans to use a particular selected vaccine strain or reassortant. This will help us. CBER will make every effort to assure timely availability of reagents appropriate for the selected vaccine strain.

Again, the CFR H1N1 in B/Brisbane reagents, if the committee approves the same strain, we have the reagents which we had provided last year. Some of the reagent lots may change. In that case, new lots will be provided. And we would request the users that please notify CBER of any problems if you face with the reagents.

And lastly, CBER contact for requesting reference standards and reagents is via an email to CBERshippingrequests@fda.hhs.gov.

Again, in closing, I want to emphasize that we at CBER are committed to make every effort to assure that reagent appropriate for selected strains are made available in a timely manner.

We believe that making the influenza vaccine available in a timely manner and ensuring vaccine consistency is a responsibility shared by all of us here.

Thank you for your time and attention and I will be happy to answer any questions.

CHAIR DAUM: Thank you, Dr. Joshi. Since we are so far behind, again, we will ask if there is one or two clarifying questions only. And then we will move on.

Dr. Englund.

DR. ENGLUND: Yes, I just have a question specifically addressed to the H3N2, of which we have seen significant, at least amino acid and some antigenic and some functional differences between cell-grown and egg-grown. And as you move forward -- I would like to know with the vaccine manufacturers, too, but as you move forward, what are you doing? Are you going to have egg-grown versus cell cultured-grown reagents? How are you going to handle that? I think it is important.

DR. JOSHI: Yes, so this is similar to last year for testing the potency of cell-grown vaccine, we make reference antigen specific using the cell-grown material. So, it is a platform-specific reference antigen prepared. So, that is why they are called the homologous antigen, derived from the same platform.

CHAIR DAUM: But it is a good question. You might want to ask the same question of the manufacturers who are speaking next.

Is there any more questions for Dr. Joshi? Then, I will say thank you very much.

DR. JOSHI: Thank you.

CHAIR DAUM: And I will see if Dr. Lee is around. Dr. Lee, you are around. And we will have comments from the manufacturers from Dr. Lee, all of the manufacturers he represents. It is all task. He is the Senior Director of the Pandemic and New Influenza Products, Franchise and Product Strategy at Sanofi. Welcome, Dr. Lee.

DR. LEE: Thank you. Thank you for this chance to share an industry's perspective of the influenza vaccine strain selection process. As Dr. Daum mentioned, I am making this presentation on behalf of all influenza vaccine manufacturers supplying the U.S. This includes AstraZeneca, bioCSL, GSK, Novartis, Protein Sciences, and Sanofi Pasteur.

As vaccine manufacturers, we do consider ourselves partners with you in the service of public health in helping to protect individuals against influenza. We appreciate the significant challenge you face to decide in advance which strains to include in a vaccine that will be prepared and used over six months from now.

I would like to characterize this challenge as a balancing of a three-legged stool. Most importantly, of course, is we want a vaccine that is well-matched to circulating influenza viruses in the next influenza season. Although vaccine mismatches can occur and do so, rarely, published studies indicate influenza vaccines in most years provide protection against laboratory-confirmed influenza in the range of 60 to 70 percent. The fact that increased incidents of influenza is observed when a mismatch occurs, confirms that influenza vaccines are quite effective.

Of course, the longer we wait to make a decision for which strains to include in the vaccine, the better our chances for getting that right but having a well-matched vaccine is only part of the challenge. We also need to produce and distribute the vaccine an immunize people before the influenza season. The problem is, we cannot predict when the influenza season will start. In some years, significant incidence of influenza doesn't start until mid- to late December. In other years, the influenza outbreaks can start as early as late October or early November.

So, while having a well-matched vaccine produced and distributed before influenza season is tough enough. We also have a third challenge, which is to have enough vaccines to immunize all those for which the vaccine is recommended.

In 2014, over a 140 million doses of influenza vaccines were distributed in the U.S. and getting that much vaccine produced, released, distributed, and administered takes a lot of time and effort.

So, we want a well-matched vaccine. We want it well before the influenza season. And we want enough of it to get everyone protected.

I know I don't need to tell you about the significant public health impact of influenza each year, with hospitalizations potentially exceeding 400,000 individuals and resulting in nearly 49,000 deaths in the U.S. alone. Because of the seriousness of influenza disease and the fact that vaccination is the best way to prevent influenza illness, the ACIP recommends annual vaccination against influenza for all persons six months of age and older, unless contraindicated. However, even after decades of effort, immunization rates remain relatively low, at roughly 40 percent overall. In fact, increasing influenza immunization rates is a specific goal of Healthy People 2020. So, in order to minimize annual burden of influenza and protect as many people as possible each year, we need to produce and distribute as much vaccine as possible before the upcoming influenza season.

To complicate things further, we have to deal with a clearly observed phenomenon that for some reason the pace of influenza vaccination seems to drop off quickly after Thanksgiving and continues to taper in December.

Plotted on this graph are medical claims data from the last two completed immunization campaigns starting in 2012 and 2013. While we can't get actual immunizations data, we can get information about the number of medical claims submitted each week, which follow the immunization trends, possibly shifted by one or two weeks.

As you can see, the data suggests that after a peak in early October, the rate of vaccination begins to fall and slows significantly by December. Despite decades of effort by the CDC, healthcare providers, and manufacturers, we can't seem to get vaccinations to continue in a significant way beyond the end of the year. What this means is we have a finite window, an endpoint to produce and distribute influenza vaccines each year.

So, with strain selection at one end and vaccinations at the other, we all have a lot of work to do each year to produce, test, release, and distribute hundreds of millions of doses of vaccine each year. In order to achieve this, as you have heard earlier, many manufacturers begin production of at least one strain at risk prior to the strain selection meeting. Shortly before, but often after this meeting, the new candidate vaccine viruses are distributed to manufacturers to produce their working seeds that will be used for production. Overall, the total

number of doses that can be produced each year is limited to the yield of the least productive of the three or four strains of the vaccine. As the various vaccine components are produced, the material can be formulated, filled, and packaged.

Besides strain selection, however, there are two key milestones. First, in order to determine how much of each component to add, the vaccine, in a process we call formulation, we need potency reassay reagents. So, these reagents are prepared and standardized by CBER, as you heard in the previous talk and typically takes over 12 weeks. So, when a new strain is selected in early March, reagents won't be available until early June. And subsequent reformulation of vaccines can't start until June.

The second milestone is the license approval of the annual influenza vaccines, which typically occurs in early July. Until that point, we cannot print the labels, cartons, and package inserts for finishing the vaccines. So, once the license are granted, packaging begins in earnest, with finished doses of vaccines beginning to roll out the door in late July or early August, about 18 to 20 weeks after strain selection. As a rough estimate, the entire U.S. supply of about 140 million doses will take about six months to produce, which is equivalent to over ten million doses every two weeks.

In recent years, the strain selection meetings have shifted by two weeks from mid-February to mid-March. What this means is that the entire

process shifts. With most vaccinations being completed by the end of the year, a shift of vaccine availability could mean a reduction to the number of people who will have the chance to receive influenza vaccines and a decrease in immunization rates. At a high level, if 140 million people are vaccinated over four months, two weeks represents about 16 million vaccinations. Whether or not this actually translates into that many people going unvaccinated, the important point is a window of opportunity is reduced by over ten percent.

So, what can we do to improve strain selection and provide some flexibility? One opportunity is to provide earlier access to potential new viruses that are being considered. If vaccine manufacturers could get potential candidate vaccine viruses earlier, we could begin working with them to understand their suitability for production and to work on improving productivity. With manufacturers ready to produce several different strains from different genetic and antigenic groups, you could have more options for selecting better matching strains.

Another opportunity is start producing potency assay reagents earlier. Of course without knowing which strains will be selected, antisera for several strains may need to be started. But having reagents in progress for several different strains would, again, give you more options for strain selection.

Now for the 2015-16 Northern Hemisphere vaccine, manufacturers have already evaluated several candidate viruses, which are

listed on the next two slides. I won't read through all of them for you but I have provided them here for your reference.

On slide seven, you see the strains are considered for A strains and in slide eight, the B strains.

In summary, then, I want to repeat that we view production and supply of influenza vaccines each year to be a shared public-private responsibility and we feel honored to be part of that process. We know that the challenge of making strain selections is to balance at least three goals but fully appreciate that influenza viruses can mutate at any time. If strain selection were shifted by a week or more, the viruses could still change after that. So, shifting the strain selection training may not be the optimal solution. We also know that in order to achieve Healthy People 2020 goals, we must increase seasonal influenza immunization rates in all age groups. So, with the influenza vaccinations tapering off in December each year and a concern about impacting immunization rates, we encourage strain selection not to be delayed or shifted further in future years. As an alternative, we suggest that we explore ways to provide more options for strain selection by sharing more potential candidate viruses with manufacturers and to start antisera preparation as early as January or early February for potential new strains.

Thank you once again for the chance to provide an industry's perspective. We wish you wisdom as you make your evaluations and decisions for the 2015-16 influenza vaccine strains.

Thank you.

CHAIR DAUM: Okay, Dr. Lee, thank you. We have a minute or two for clarifying questions for Dr. Lee's talk. I guess I will start off and ask whether knowing what you know right now, you will be able or not be able to deliver vaccine in time for next year's flu season, given the strain selection that is likely to occur this afternoon.

DR. LEE: Well, based on the experience that we had from the Southern Hemisphere campaign, the productivity of the viruses do appear that they are sufficient for providing enough vaccine for the U.S. supply this year. Assuming that the strains aren't different from those selected from the Southern Hemisphere also recommended by the WHO.

CHAIR DAUM: I kind of thought so but I wanted to hear you say it.

Any other questions or comments? Dr. Long.

DR. LONG: I will ask Dr. Englund's question because she is very shy. So, do you --

CHAIR DAUM: That has not been my experience.

DR. LONG: -- plan to monitor as you go to be sure that the vaccine you are producing is the antigenic equivalent to what you started with, seeing what we know about, especially changes in egg propagation?

DR. LEE: So, the vaccine viruses that we use for manufacturing are all tested and released or certified by the FDA. So, the viruses that we use to start the production process, each batch of that, each batch of those viruses are actually samples are sent to the FDA. They are tested and confirmed that they are antigenically similar to the reference virus and also to the wild type virus that is selected for the composition in the vaccine.

CHAIR DAUM: Last question, Dr. Edwards.

DR. EDWARDS: If, indeed, we could have used the crystal ball to predict that the strain was not going to be the match and would not, ultimately, be very effective, would it have been possible in February to generate a monovalent vaccine that was matching the strain that was circulating and administer that as we did with the pandemic vaccine?

DR. LEE: I think the challenge with that is -- it certainly is possible and we have demonstrated that we were able to do that in the past. The challenge is having sufficient number of doses, while you are also producing the seasonal vaccine, as well as an additional vaccine. Because it certainly doubles

up in terms of several steps in the process, specifically, in the formulation filling and packaging piece of the process.

DR. LEE: Does that answer your question, Dr. Edwards?

DR. EDWARDS: Sort of.

CHAIR DAUM: Dr. Englund, last question.

DR. ENGLUND: I just want to go back to the antigenically similar, which goes back. I understand that is really important but now we know that there are amino acid changes that actually effect things such as function. I am just wondering what more should be considered to prove that we have a vaccine that not just is antigenically similar but since the vaccine strain could have been passed in eggs and may actually be somewhat functionally different, not just you the manufacturer, but you the influenza community, what other testing is being considered in light of the really broad perception in the public that we aren't doing enough?

CHAIR DAUM: Thank you, Dr. Englund. Thank you, Dr. Lee. Did he not say it?

DR. LEE: No, not yet. I guess I am thinking that I am probably not the most qualified to respond to that. But my understanding is that the reference candidate vaccine viruses that are recommended and provided to manufacturers are those that best represent from an egg-produced as well as a

cell-produced vaccine. So, they do provide broad coverage from both types of technologies. That is my understanding of the recommended viruses and those that are provided to manufacturers.

CHAIR DAUM: Okay, thank you, Dr. Lee. Dr. Lee, thank you very much.

DR. LEE: All right. Thank you.

CHAIR DAUM: It is now lunch time. It is also now 12:15 in the Eastern Time Zone. We will take a 30-minute lunch.

For committee members, the lunch down in the restaurant is in a buffet. There is a table reserved for committee members that we have just been arranging while Dr. Lee spoke. You will take your buffet lunch, sit down, and then someone will come over to you and collect the money. They have already got the money, of course. So, once that is done, you enjoy your lunch and come back in 30 minutes.

We will start at 12:45.

DR. VIJH: I just have one comment for the public. After the lunch break, we have the open public hearing at 12:40. Could you please, if you have showed any interest before the meeting to make comments and you haven't signed up yet, could you please sign outside? And if you wish to speak, please sign outside so that we have an idea who is going to be talking. Thank you.

(Whereupon, the above-entitled matter went off the record at 12:15 p.m. and resumed at 12:52 p.m.)

CHAIR DAUM: It's time for the open public hearing. I have a statement that I am required to read and I will read it now.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of the statement, it will not preclude you from speaking.

And with that, there are three people scheduled for open public hearing statements. I will call on them in due time. The important thing for the committee members to realize is this is not a question and answer session for

the committee. So, the open public hearing speakers will say their piece. We will thank them and then move on.

The first open public hearing speaker is Cynthia Bristow from Alpha-1 Biologics and Stony Brook University, New York.

Is it Dr. Bristow or Ms. Bristow?

DR. BRISTOW: Dr. Bristow, thank you.

CHAIR DAUM: Dr. Bristow, welcome.

DR. BRISTOW: Thank you. First of all, neither myself, my company or any of the institutions that I am affiliated with now or in the past, nor any of my family members will benefit from any of the comments that I plan to make here today.

Does that satisfy the statement that you need to hear?

CHAIR DAUM: It certainly does.

DR. BRISTOW: All right.

CHAIR DAUM: You have to remember, though, that no statement would have satisfied.

(Laughter.)

DR. BRISTOW: I am an immunologist, formerly a faculty member at The Rockefeller University Mount Sinai School of Medicine and Weill Cornell Medical College. I am now CEO of a small company Alpha-1 Biologics, which is affiliated with Stony Brook University.

I am here to propose that we evaluate the optimal ages for childhood vaccinations. The 2015 CDC recommends that beginning at two months of age infants be vaccinated with weakened live rotavirus, followed by vaccination at 12 to 15 months of age with five weakened live viruses, including flu, measles, mumps, rubella, and chickenpox. These weakened viruses each cause a mild infection. Considering that the MMR contains three viruses, a 12 month old child vaccinated according to the CDC schedule would receive on the same day five live viruses, causing five mild infections. Maybe this is safe for two-month-old and 12-month-old children but the safety of inducing this many mild infections at these ages needs to be evaluated and for a period longer than the standard few weeks of follow-up.

Of extreme importance and not well-recognized is that the immune system and central nervous system are sister organs. The two systems evolve together, are immature at birth, simultaneously mature, use many of the same chemical messengers, and maintain memory.

Also not well-recognized is that 70 percent of the brain is composed of specialized immune cells called glial cells, which provide the sheath

that insulate nerve cells. Without a sheath, nerves are unable to transmit messages. Recent evidence shows that one type of glial cell is abnormally activated in autism spectrum disorder. There is ample evidence that, although rare, measles, mumps, and rubella viruses can infect glial cells, causing inflammation of the brain and serious neurologic problems of the unborn child, as well as, according to the CDC, 28 percent of children under five years of age.

The chickenpox virus is a herpes virus that infects nerve cells and can also cause brain inflammation in the unborn child and in children under the age of 12 months. Rotarvirus infects cells in the gut, causing severe diarrhea and remitting milk intolerance.

Because children often enter day care as infants, it is clear that the CDC recommended vaccines are necessary and desirable. However, considering the immaturity of the immune system and brain from birth to two years of age, this presents a challenge. How do we know whether providing immune protection to these children is not too early in the development of their brains, immune systems and digestive systems?

Knowledge of the developing brain has been achieved by brain imaging, methods not available when the FDA approved some of the CDC-recommended vaccines. The CDC reported in 2004 that autism spectrum disorder affected one in 166 children and ten years later, in 2014, an alarming one in 68. Because the MMR has been administered to greater than 90 percent

of the U.S. population for more than 50 years, it is highly unlikely that MMR could cause the increase in autism spectrum disorder. However, the safety of this and other vaccines can be tested at least in animals before vaccination and several times after vaccination over a period of several years. Such a study would confirm whether vaccination is safe at the recommended ages and of equal or greater importance, it may help reveal the true cause of autism spectrum disorder, a scourge that is increasing and, as of yet, has no known causes and no known preventions.

Thank you.

CHAIR DAUM: Dr. Bristow, we thank you.

Our second open public hearing speaker is Margaret Dayhoff-Brannigan, for the National Center for Health Research. Is it Dr. Dayhoff-Brannigan or Ms.?

DR. DAYHOFF-BRANNIGAN: It is Doctor.

CHAIR DAUM: Thank you, welcome.

DR. DAYHOFF-BRANNIGAN: Hi, my name is Doctor Margaret Dayhoff-Brannigan and I am a senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy-makers.

We do not accept funding from pharmaceutical companies and I, therefore, have no conflicts of interest.

Thank you for the opportunity to speak here today. I completed my Ph.D. in biochemistry and molecular biology at the Johns Hopkins School of Public Health. I bring a perspective as both a researcher and an advocate for public health here today.

An effective flu vaccine is critical for public health. Antiviral medications have very limited efficacy. So, for many people, the flu vaccine is the best line of defense to protect against infection.

The CDC's latest report calculated a 19 percent vaccine efficacy this year. That is simply not good enough. More importantly, this is not just one bad year. Four of the past ten years, the vaccine has been less than 40 percent effective.

When the flu vaccine does not work well, people think they should not bother to get it. This is bad both for the pharmaceutical companies, who have unused doses of vaccine and for the general public that is less protected. It is important that we implement strategies to improve the efficacy of the influenza vaccine.

According to the briefing information, a new strain of influenza A, H3N2 was detected in March 2014, after last year's vaccine production had

already begun. Nothing has changed in response to this new data. We urge the FDA to consider changing the time line for selecting strains for the vaccine to allow more time. We understanding there are tight deadlines but there should at least be a strategy for making a last minute change to one of the strains selected for inclusion, if it is found that there are newer circulating strains within a certain time frame.

In response to the 2009 H1N1 pandemic, vaccines were produced in an accelerated time line. So, we know that this is possible. While these strategies may cost more to implement, the increased cost is worth it, if efficacy could be substantially improved. More effective vaccines will save lives and will save money and reduce sick days taken, doctor visits, and hospitalizations.

Currently, there are few incentives for pharmaceutical companies to implement strategies to improve vaccine effectiveness. For example, military healthcare, childcare, and teachers will all be required to get flu vaccines next season, regardless of how ineffective the vaccines have been this season.

In addition, the FDA should look carefully at whether the live attenuated vaccine, or nasal spray, should still be approved, since, for the second year in a row, it has shown considerably lower efficacy than the standard flu shot. At the very least, the nasal spray label should specify how ineffective they are, compared to flu shots.

We urge the FDA to require new protocols to ensure that the best and most effective vaccine is produced each year. Thank you for your time.

CHAIR DAUM: Thank you, Dr. Dayhoff-Brannigan.

Our third and final speaker at the open public hearing is Matthew Downham. Is he here from AstraZeneca? Is it Doctor?

DR. DOWNHAM: Yes.

CHAIR DAUM: It is. Then, welcome, Dr. Downham.

DR. DOWNHAM: I will be honest. I am a little confused. I didn't realize I was going to be speaking today. So, fairness --

CHAIR DAUM: I think you signed up for it.

DR. DOWNHAM: I didn't. I didn't. I'm sorry.

CHAIR DAUM: If you want to not speak, that is fine. I am sorry about the confusion.

Okay, that concludes the open public hearing, ladies and gentlemen.

I want to resume the committee discussion, voting and recommendations. And I want to inform everybody that Dr. Kathryn Edwards had to leave and take an earlier airplane.

So, we will now have committee discussion. And then, when I sense that people are starting to say the same thing more than once, we will go to the voting.

We will conduct votes on each strain that are put into the vaccine. Sujata is ready to run the voting when we reach that time. So, first, we will have comments, if there are any, on any aspect of flu immunization you wish.

Dr. Gellin.

DR. GELLIN: So, this is a question I wanted to ask Jackie when she was at the podium. The cartography is a lot easier to digest for the people who are not literati. So, thank you for that.

I wonder, in your world, do you have a radius that you look at and think of which things are within and out of the radius? And then the question is then what do you do with the other players that are either inside the circle or just outside the circle?

DR. KATZ: Well, I think we use the same general radius that we would for the actual HI data because each one of those squares is supposed to represent about a two-fold difference. So, once you move beyond the four-fold difference and you see clusters of virus, and I think the good thing about the antigenic cartography, it is very visual, you can see the scatter and the variability of the data, but certainly once you are, whether it is vertically down or diagonally,

and I don't quite understand in the different cartography sometimes, things are very distinct but they may be on a diagonal versus on a vertical axis. But it is generally, once there is an eight-fold difference, you very clearly see the clear separation and the example is this year the difference, the antigenic cartography, because it is a program that keeps running and using certain reference viruses, it is more able to visually see these difference sometimes and the B/Yamagata lineage virus is an example of that.

CHAIR DAUM: Dr. Sawyer.

DR. SAWYER: That was my question also for you, Dr. Katz, is that the cartography really strikingly shows evolution of Yamagata B strains from 2013 to 2014. But the two tables, your table 5.8 and 14.7 is very hard to see much difference.

Is the data derived from the same sources or how do we account for the difference?

DR. KATZ: It's a good question and it is, again, because of the -- when we just look at the HI data, we see a lot of four-fold differences. But in the processes that they use, it is a modeling strategy, they can focus on certain sera that, I think, really show the greatest difference. And so, I think it is a more focused approach.

And I think I also mentioned in my talk that for the B Yamagata lineage viruses, particularly some of the centers, there seems to be a greater sensitivity of the ferret antisera that is used. And there has been some subtle differences between the centers so that some of the centers in London and Melbourne, their reference antisera tends to separate things out a little bit better than the CDC sera. But when it is put into the antigenic cartography, it becomes clearer.

And I'm sorry, I can't really explain it any better than that.

CHAIR DAUM: Thank you. Dr. Hudgens.

DR. HUDGENS: Yes, I wanted to follow up on that. Dr. Grohskopf had a slide, slide four or six, where she showed that --

CHAIR DAUM: Is she here?

DR. HUDGENS: So, in her data, 94 percent of the viruses characterized were Massachusetts-like. And so that would suggest not switching the Yamagata vaccine strain --

DR. KATZ: Right and I made that point at the end of my talk, that this was based on the CDC data. And using our ferret antisera to Massachusetts, although we saw an increasing number of viruses that had reduced titers, we didn't see what two other centers were seeing where the majority of viruses were now low to the B/Yamagata -- I'm sorry to the

B/Massachusetts/2012. So, that is focused. Dr. Grohskopf's slide is based on the CDC HI data.

And as the gentleman next to you said, it is not as clear with our reference ferret antisera. We can see that the antisera to B/Phuket covers better, covers viruses better now than the B/Massachusetts does. And in other centers, it is much clearer than that.

DR. HUDGENS: Just so I am clear, you think this is due to differences in labs and not regional differences.

DR. KATZ: I believe it is due to differences in the production of ferret antisera. And we have seen that for different viruses that we may not always get exactly the same profiles and that is why we do this multiple times in multiple laboratories.

CHAIR DAUM: Other comments? Dr. Piedra.

DR. PIEDRA: Yes, and this will be for Dr. Katz. Historically, the H3N2 has been associated with the highest mortality and an example is of this past year. And I was wondering how much time can there be a delay in the selection of H3N2 viruses in particular, so that we have the optimal match in the vaccine, since the H3N2 viruses tend to have the highest mortality rate in the general population.

DR. KATZ: So, you are saying make a recommendation for the other strains and then wait as long as possible for the H3. Is that --

DR. PIEDRA: Correct.

DR. KATZ: I think that is one possibility. It would need a lot of coordination and then, as you know, the timing is very critical. We would, the other critical thing is even if we have made a recommendation, it would be, if we delayed it, we would certainly want to know that we had a viable egg-grown candidate at that point and that we had good characterization and that it had good properties, if we were going to go down that road and delay H3N2. It might buy us a bit more time. But in some years, H3N2 is not going to be the predominate strain.

CHAIR DAUM: Is Dr. Lee still here for the manufacturers? Could you comment on this issue of delay?

DR. LEE: Could you repeat that last bit?

CHAIR DAUM: So, I am asking you to comment on -- the question has come up from Dr. Piedra about possibly delaying selection of one of the vaccine antigens. And I am going to paraphrase and say one or more of the vaccine antigens.

DR. LEE: Right.

CHAIR DAUM: Dr. Katz has spoken her piece and I would like to hear your piece. Does the manufacturing community support this kind of delay and how would you orchestrate it?

DR. LEE: Right. So, any delay of course changes the whole dynamic. And as I illustrated in my chart is that there is a shift --

CHAIR DAUM: One moment. The microphone is not on.

DR. LEE: Oh, is it not?

CHAIR DAUM: It's on? It's not loud enough, then.

DR. LEE: Okay, is this better?

CHAIR DAUM: Much better.

DR. LEE: Okay, as I tried to illustrate in my chart there, any shift in the timing of strain selection shifts the entire process. So, if there is a shift of two weeks or however many weeks, the entire process would shift and you would potentially lose vaccinations at the tail end of the vaccination period. It also affects the start of the early doses that are made available. What it didn't talk about is the need for vaccines in the August period because many of the students and the kids are actually vaccinated before school, the preschool period. And that is where it is critical to have sufficient vaccines for that school-aged children group that is vaccinated in August.

CHAIR DAUM: Dr. Piedra, do you want to follow-up on this or no?

DR. PIEDRA: Well, my fear is that public trust is, I think, something very relevant, whenever you have a universal influenza vaccination policy. And if we don't choose wisely the vaccine antigens and we don't have good effectiveness, we will lose that public trust. And so in today's modern society, it is hard for me to believe that we cannot do better than what we are doing. And we know, historically, H3N2 has been the virus that is always associated with highest mortality. And again, this past year is a nice example of that.

And so if there was a virus that one had to delay, I would think of the H3N2 and think of how one could work with FDA, industry, CDC, and others in trying to streamline that process.

CHAIR DAUM: So, based on what I heard this morning, people in the audience like Dr. Katz and Dr. Lee can contradict me, if they wish. They really didn't know that this new H3N2 strain was a presence, a major component of H3N2 and a major cause of disease until the summer was, virtually, over.

And if that is true, I wonder what, I mean I am sitting here and I came in thinking that, God, we can do better, too, but I am not so sure now, given what I have heard and given this H3N2 scenario. So, maybe your comments on that would be appreciated.

DR. PIEDRA: We know that we have not had good antigenic match on some years. And I wonder whether we can go back in time and look at whether we would be able to predict that, knowing what we know at this time. Is there -- and I leave this really to the CDC and FDA to provide advice there. I don't know what would be the paradigm to do that.

CHAIR DAUM: It sounds difficult to me but desirable.

Yes?

DR. DUBOVSKY: I was just going to make the point that different manufacturers have different processes they need to follow. And what may actually work for one may not work for the other two. Delaying one strain, a single strain may actually have a huge knock onto the entire process of how the logistics of getting the vaccines manufactured, labeled, shipped, all of that, it is very tightly coordinated.

So, I wouldn't discount even a short delay having a pretty big knock down effect downstream.

CHAIR DAUM: So, that is another manufacturing point of view. I see Dr. Levy and Dr. Englund. Maybe Dr. Englund first, then Dr. Levy.

DR. ENGLUND: I think I understand this group understands somewhat the complex -- we don't understand it all but we understand the time that it takes.

But this is an example where, it is my understanding that the Southern Hemisphere vaccine was chosen way back in September. The vaccines are manufactured. Are we getting any data at all in humans to see?

DR. KATZ: I don't think it has gone into humans yet. Not as of last week, anyway, when I asked my Southern Hemisphere colleagues.

CHAIR DAUM: Could you say it again, Dr. Katz? I didn't hear it.

DR. KATZ: So, I don't believe any of the Southern Hemisphere vaccine, which contains the Switzerland 2013 component, I don't believe that any human vaccination trial studies or just public vaccination has begun yet. And then you need illness, of course, to see effectiveness.

CHAIR DAUM: Thank you. Dr. Levy.

DR. LEVY: Among the things that struck me from this morning's presentations and they were all excellent. Obviously, it is a huge amount of work and a huge good faith effort to do the best possible under a difficult situation with a difficult time line. But what struck me was the consideration of the leveraging of the in vitro assays which are important and, at the same time, viruses changing and some assays may or may not be possible, depending on the type of virus, whether it is binding red cells.

And it would seem interesting and perhaps pertinent if FDA were interested in convening a separate meeting to take apart what the data looked

like year on year, how these systems are performing, these in vitro approaches year on year, as virus changes and what are the possibilities for improving the systems for the future. It is almost a separate question because the task at hand now is to decide on strains to include in a vaccine. But there are deeper questions because this is a pattern, obviously, for a yearly decision process that relies on certain types of information and maybe a meta-analysis over the past ten years of how those systems are performing is in order. You also have the differences between the egg-based and the cell culture-based, et cetera. And I think there is nuance and importance in that data that we don't have time to really take a deep dive into right now.

CHAIR DAUM: Thank you very much for your comment. I am going to ask Dr. Weir to respond for the FDA.

DR. WEIR: Yes, your comment about another meeting to look at the different assays and pieces take this apart, I just want to remind those of you who know and those who don't, the WHO has had three meetings over the last three years on this very subject about improving strain selection. All of us, the FDA, the CDC, have been heavily involved in that. I think CDC sponsored the meetings, if I remember right. And anyway, the purpose was to examine all of the different techniques that are used, the pluses, the minuses, what they are good for, looking for ways to improvement.

And anyway, it is an ongoing process. There have been three of these. There will probably be a fourth one in the next year. So, it kind of is an ongoing process to look at all of these aspects. I think the end result is that there are a lot of things on the horizon that show promise. And I think that they will be incorporated, at some point, when they are ready.

DR. LEVY: And to sort of piggyback on that is also the notion that we don't fully understand how these vaccines are acting and the different formulations get lumped together, for some analyses, based on what strains are there but they are prepared in different ways, whether they are -- you know depending on the manufacturer and what exactly their properties are in terms of innate immune activation, if any, is not really well-understood. So, that is another area because that could also impact vaccine efficacy.

DR. WEIR: That is maybe true but it is true that all of the licensed vaccines are based on hemagglutinin and I think we do understand pretty well the responses to HA in all of the vaccines that we have licensed.

DR. LEVY: Yes, no, that is the antigen but what else is in there and what is it doing to the early antigen-presenting cell phase of the response. As we know, you know, adjuvants has the dirty little secret of vaccine production. What else is in there and how might it be shaping a different immune response to these kind of questions? I am not sure I have seen that in the literature.

CHAIR DAUM: Dr. Bennink?

DR. BENNINK: Yes, the first comment I would make is that I would encourage the CDC, through their network, as well as the military to take out further the levels so that you can discriminate aspects of severity, in terms of vaccine efficacy because I think there may be further discriminations of how well a vaccine is actually doing something. If you get other discriminators to try and take it out and not just say okay, I have got a confirmed flu infection or something along that line and some coughing or something else that does it. So, if you do that, it may help to discriminate some of that.

A couple other questions here. But you know I thought Dr. Moore came with some of the data that we saw here early this morning in terms of immunogenicity of these new strains that are being considered and stuff. Do you have any idea about what that really looks like? Because on a couple of the data slides that were there, some of the data for the Phuket, as well as the Switzerland looked like they were relatively low in some of the data, compared to some of the other aspects that are there.

And is that something that may be true or not? Because if the FDA is still looking at, what is it, a titer of 40 or something, the level, the four-fold or eight-fold from something that is super high in terms of immunogenicity versus something that starts at 160 is significantly different, in terms of that. Is there any idea at all about what the immunogenicity of these different strains are?

CHAIR DAUM: Dr. Katz, do you want to respond to that?

DR. KATZ: Sure. Yes, just going back to the question of the morning about the relatively lower homologous titers with ferret antisera to some of the viruses, including Switzerland, I would be really cautious to interpret that in any way with respect to vaccine and immunogenicity. I just don't think we can do it at this time. And unfortunately, I think, as Dr. Ye from FDA mentioned earlier, and I just mentioned also, we really have no idea of how the Switzerland virus, how immunogenic or not it may be in humans. That we make decisions every year without that information, in general. I mean when we do a strain change, we don't have that information yet, unfortunately.

CHAIR DAUM: Go ahead.

DR. BENNINK: To continue another thing, it didn't look like the Swiss covered the 2a very well, except for the cell-based vaccine in that respect. It didn't look like it was quite as good. But the only one that was tested was it a Hong Kong or something that was egg-based and that didn't show cross reactions very well.

DR. KATZ: That's right. That is the 3C.2a group. That was the only egg-grown virus for which we had or the WHO collaborating centers had a substantial dataset. And although the cell-grown Hong Kong virus antisera raised to that virus covered circulating viruses quite well, the egg-grown virus didn't at all.

In contrast, the Switzerland, the 3C.2a, again, the antisera raised to the cell-grown covered the majority of viruses, and again, this is CDC HI data, about 85 percent of the viruses. And it was slightly less with the antisera raised to the egg-grown Switzerland. It was about 71 percent of viruses.

CHAIR DAUM: And Dr. Levandowski -- oh, sorry. Do you want to follow-up? Dr. Levandowski.

DR. LEVANDOWSKI: Well, I want to switch focus to something else.

Influenza B, I would like to go back to some of the data for the B/Victoria strains of influenza B and just preface the statements that I am going to make with actually influenza B component of the vaccine is the one that seems to be the most problematic in terms of effectiveness and efficacy but it is very important and particularly in children. And children are part of the reason the vaccines are being made quadrivalent so that they can have an immune response to both of those influenza B hemagglutinin lineage viruses that are still circulating and co-circulating a lot of the time, although they don't seem to be doing much co-circulating right now but that is part of what I wanted to bring up.

If you look at page 19 of the CDC handout about the global circulation of influenza B viruses, what it shows, I think, I mean most of those viruses are not typed as to whether they are B/Yamagata or B/Victoria, but you see there are little blips each year of one or the other of the two HA lineages.

And over the last four years, B/Victoria has been the one that is pretty much not causing a lot of problem. It is mostly B/Yamagata. Whereas before that, for a couple of years, it was the B/Victoria strains that seemed to be predominant. So, there is some flip-flop there in those strains. And since it has been four years since B/Victoria has been predominant, it seems like we might be due for one of those. I mean predictions are always bad for flu. Everybody tells you don't try to predict because you can't. But the number of people who have been exposed to B/Yamagata-like strains as compared to B/Victoria strains, the population is building up that will be susceptible.

And there have only been a few of these B/Victoria strains that have even been collected since 2011, I guess. And I don't remember how long B/Brisbane/60 has been in the vaccine but it is five or six years. It is getting a pretty long time.

Dr. Katz gave us some information about the CNIC data for strains that didn't seem to be, or there seemed to be some B/Victoria drift going on but it was a little bit difficult to explain and dicey for some technical reasons that are not entirely clear.

And then, finally, if you go to the CDC handout, page 25, there is information there that shows that as compared to the B/Brisbane strain itself, the B/Texas strain seems to give coverage against more recent and particularly more recent U.S. viruses that have been isolated in 2014 better coverage against

those, comparing the homologous and the test antigens better than the B/Brisbane does.

So, one thing that I guess would be nice to have would be more human serology. There was only the B/Texas strain that was included in the serologies. I know that is from 2013. None of the more recent 2014 and B/Victoria-like viruses from the United States tested.

But I guess where I am going with this overall is that there seems to be a lot of data that suggests: 1) we are due for something to change antigenically with B/Victoria, including the puzzling data from CNIC; 2) the vaccine strain may not cover the more recent B/Victoria-like viruses that well, particularly in the United States. And I think it is maybe a consideration to find a virus like B/Texas that might give a little bit better, broader coverage.

CHAIR DAUM: Dr. Katz, do you want to comment on that?

DR. KATZ: I think Dr. Levandowski has a good point. If you look at the cycling of the viruses, it seems like we may be due for a B/Victoria season but it is very hard to predict. For many years, B/Victoria was only seen in Asia. So how it popped out and spread to the rest of the world, then why it has really only circulated at lower levels, it is difficult to understand. But I think he makes a good point about the more contemporary Texas virus, which is a B/Brisbane-like virus is in the antigenic group that we are seeing amongst the B/Victoria viruses.

And it would be up to the committee to make a decision as to whether they would actually identify a strain, I guess.

DR. YE: I just would like to comment on the Victoria lineage. Although the B/Brisbane/60 is the virus being recommended for many years, however, Texas/02/2012-2013 is similar to Brisbane/60 being considered as Brisbane/60-like. Some manufacturer already used that one as the predominant as well. And also in the WHO Collaborating Centers and the lab who generated the vaccine viruses keep adding Brisbane/60-like viruses as vaccine candidates. So, it is being said that the Brisbane/60 virus is being updated with the newer viruses.

CHAIR DAUM: So, what is the bottom line, Dr. Ye? What is your recommendation?

DR. YE: My recommendation is that although the Brisbane/60 is the old vaccine virus, however, a new Brisbane-like virus, which is a new isolates are being considered and being generated as a vaccine candidate for manufacturing uses.

CHAIR DAUM: Thank you. Other comments? Dr. Bennink.

DR. BENNINK: So, I want to go back just for one quick question. Jackie, are there other viruses that the CDC is working on in the 2a group, like Michigan or some of these other ones?

DR. KATZ: Right. Unfortunately, at CDC, we have not been able to isolate any of the 2a viruses in eggs. The Australian Collaborating Center does have a number of candidates that it has, I believe, sent to reassorting labs. And there was another candidate, a New Caledonia/71/2014 and that was the second 3C.2a egg-grown virus that I briefly referred to. But as you see, there was no data on that virus in my package. And that is really, unfortunately, where we stood. It was a very recent virus. There is a reassortant but the group at WHO last week felt that we really had too preliminary and too insufficient data to recommend that as a vaccine virus.

So, there are others in the works but timing is the issue here. And we don't know how long it would take for the viruses, first of all, to have a successful reassortant to pass the so-called two-way antigenic test that is required for a virus to become a candidate vaccine virus.

And the other issue of concern was that like the Hong Kong virus, all of the viruses that had been isolated in eggs, wild type viruses that had been isolated in eggs from Australian group, they all contained very similar egg adaptations. And so we were concerned that they may show the same undesirable properties as was seen with Hong Kong.

CHAIR DAUM: I have a question for any of the stakeholders. And that is, do we have any data about vaccine and amelioration of illness? That is to say, are there any data that suggest that vaccine recipients, while they may

not be protected, have a less severe disease than a control group? And if not, are there plans to get such data? And then I will call on Dr. Bennink after we go through this.

DR. DUBOVSKY: There is published data looking at severity of disease that is prevented by vaccination, both from inactive as well as live influenza vaccines. And it is --

CHAIR DAUM: Can you cite them?

DR. DUBOVSKY: No, of course not. I don't know that data off the top of my head. But I would look to publications for MedImmune from, I believe, GlaxoSmithKline. What you do is you do an efficacy study and then you just parse out the more severe disease or criteria to do a more severe disease and you do a sub-analysis. And that is the way those studies have been done in the past. There are probably smarter ways to do that.

DR. KATZ: So, for example, you could look at length of fever and things like that. And I do recall that there is some perhaps GSK data along those lines. Again, you have to do extremely large studies to get any significant data.

CHAIR DAUM: Dr. Bennink.

DR. BENNINK: Yes, so I think since we are looking at this, I think at least something should be said in terms of these things. You know the CDC put out a statement on LAIV at the end of last year. And during the '13 and '14

year, there was no measurable effectiveness for LAIV against influenza among the children enrolled in the study.

And then last year, as well as this year, we have military show a negative percentages, both times in terms of some of the effectiveness of what they parse out, in terms of this.

And so I actually think that at least we should suggest to the FDA and the CDC that they revisit this and at least look at it, along with MedImmune and sit down and talk with some other experts and sort of look into this thing and figure out what is here. Is there the other effectiveness that it is less severity or something. But some of the discussions could include what is the ideal assay or measure of efficacy for the live attenuated. You know it has never really been, I don't think, at least as far as I know, exceptionally good at generating the highest titers of HI or neutralizing the antibody. And as presumed, is it immunity more cell-mediated and innate? And how could this be evaluated, other than confirmed by influenza infection and acute respiratory infection such as additional measure of severity, morbidity, or mortality at the things that we have sort of been talking about?

Is the live attenuated more effective in terms of severe illness than the subunit vaccines when circulating viruses are a significant mismatch or does a mismatch make infection worse because one was immunized with a live

attenuated? Is there any kinetic data on timing of vaccination and infection and matching of the viruses?

If the effect of immunity is based, on a large extent, on the core and the internal proteins, can there be changes in the core proteins over time that will mean the core may require a change, when it becomes less effective or something like this? Do we need to look at something different?

What is the evidence that supports this as a vaccine that should be recommended for the children above the subunit vaccine as it was done, to some extent? And should clinical studies be performed with a challenge model to assess some of these different issues?

And then some of the more recent things in terms of are there correlations with live attenuated and subunit vaccines and the generation of broadly cross-reactive antibodies or outcomes or other things like this?

I just think there should be, and maybe there already is, a discussion going on in the FDA about what is going on with these vaccines.

CHAIR DAUM: So, Dr. Greenberg, we don't normally call on people in the audience but since you are so well-respected and we know you, we will make an exception. I hope your comment is very brief and you don't expect to be questioned and answered.

DR. GREENBERG: Thank you very much, Dr. Daum.

When you posed your question just a couple of minutes ago for any of the stakeholders, I thought I would take that opportunity as a stakeholder. I am with Sanofi Pasteur.

CHAIR DAUM: And I have called on you.

DR. GREENBERG: Yes, thank you. The question about data relevant to a milder disease among vaccinated persons, yes, there is definitely published data. We can find those publications and provide them to the committee, if you are interested.

In our high dose efficacy trial, there was a reduction of severity of disease among those receiving the high dose vaccine, compared to standard dose. There are studies that have been published, in children, particularly, among those requiring hospitalization and ICU care. And it is less frequent among vaccinated than unvaccinated children. And there is a host of other efficacy studies done by other manufacturers who found similar findings.

If I could just take one second to respond to the question about delaying a decision on the H3N2 virus, that would clearly have a major impact for all of the manufacturers. If it would be a month or two before we knew what strain that would be, say a clade 2A strain, reagents wouldn't be available instead of mid- or sometime in June it would be July or August. Licensure couldn't occur until after that. Distribution would be well into the fall. We would have an entire cohort of school children who would not be vaccinated because the pediatricians

wouldn't have their vaccine available to vaccinate. I'm afraid we would have a significant fall in immunization rates this year, if we were to do that.

CHAIR DAUM: Thank you, Dr. Greenberg.

Dr. Sawyer has his hand up. I hope it is not in response to this.

DR. SAWYER: Well, it's in response to two comments from the manufacturer that school children get immunized in August. That has certainly not been my experience in my community. Especially this year, many pediatricians didn't get any vaccine until September or beyond.

So, I don't think we should make decisions about delay predicated on the notion that school children are getting immunized in August.

CHAIR DAUM: So, I guess what I would say before we move on is for the stakeholders to all listen because the committee is clearly not comfortable. What is our discomfort exactly? It is with vaccine efficacy. It is with the strain selection process. It is with the issue of partial protection. It is with the issue of wanting manufacturers to do what I think is a Herculean task of getting more than 100 million doses made in a very short time. And the public, as we know, has little appetite for aberrance and vaccine safety. So, it has got to be a 100 million safe doses.

So, I think that there are issues here that could be explored and could be discussed. We are not really in a position or suited to do it now. But I

think that stakeholders listen because I think that there is an opportunity to have discussions about this and make plans to get the data that we need to improve this process.

And with that, I will ask if anybody has any comments of things that haven't been said before. And then we are going to go to the vote and then we are going to adjourn.

Dr. Long and then Dr. Englund.

DR. LONG: Since we can't have any effect on the behavior of a virus and maybe we can't effect a shorter production of vaccine, it just seems that there ought to be all these people from the World Health Organization trying to select strains better. There must be a wealth of information in tracking these viruses through the season.

For instance, I want to know right now what is one percent of what is being isolated, been isolated in February. So, last year one percent in February were the Switzerland-like. Well, one percent in an outbreak time is quite a lot of viruses. And that is a lot different than four percent or ten percent in the off-season.

So, do you know right -- first of all, has it been we have only seen the majority in 80 something percent of H3N2 has been the Switzerland-like. Has it changed through the season?

What percentage of the virus is now, let's just take H3N2, in February are not identified as Switzerland?

CHAIR DAUM: And do we have those data?

DR. KATZ: So, I guess it would be going back to the table on page -- so the CDC table on page 15, where -- and I can only speak of the aggregate data because we haven't broken it down by month, but of the 630 viruses that we have tested, of which the majority were low to Texas, if we look at the cell-grown, response to cell-grown Switzerland, six percent are low reactors; whereas, it is about 29 percent to the egg-grown Switzerland. So, that would be the proportion of viruses that are presently low to Switzerland.

And if you compare cell-grown 3C.3a, the Switzerland with cell-grown 3C.2a, which would probably be the better comparison, then you can see the proportion that are antigenically low is six percent for Switzerland and nine percent for Michigan. So, it is about the same.

CHAIR DAUM: Thank you, Dr. Katz. Dr. Englund?

DR. ENGLUND: Yes, I actually understand and I believe that we need to be moving forward with a Switzerland-like virus, although I am concerned about how it is going to work.

But I would like to go back and hear, Dr. Katz, from the CDC. I do have the concern about continuing of the B/Brisbane, which is old, and I am

actually doing work in Nepal. I think we are seeing a lot more of other B/Vic strains. And I guess I would like -- I am not trying to rock the boat here, but looking at the data, it does look to me like we should at least be considering an updated B/Victoria-like strain.

And I would like to hear officially from the CDC. You have recommended on paper to continue with the B/Brisbane and I am wondering why we shouldn't go with the Texas.

DR. KATZ: No, I mean the WHO recommendation was for a B/Brisbane-like.

DR. ENGLUND: Okay.

DR. KATZ: Texas is a B/Brisbane-like.

DR. ENGLUND: So, we don't have to say Texas here.

DR. KATZ: It is a candidate vaccine virus. And Dr. Ye from FDA said, apparently, some manufacturers are using it. I don't know if all U.S. manufacturers are.

DR. ENGLUND: So, by saying B/Brisbane-like, that would include Texas and we don't' have to make a differential vote, is what I am --

DR. KATZ: Right.

DR. ENGLUND: Thank you.

DR. KATZ: And all I can say is that in our data that I shared with you in the HI table, the ferret antisera to Texas virus has covered the circulating viruses somewhat better than antisera raised to be B/Brisbane 2008.

DR. ENGLUND: Yes, even maybe a tiny bit more than somewhat better. So, thank you.

CHAIR DAUM: Okay, thank you, Dr. Englund, for your comment, Dr. Katz, for her answer.

And I think we have heard all the comments and we are ready to vote. If there are unsaid comments, please stick your hand up and say them now.

Dr. Gellin, an unsaid comment.

DR. GELLIN: I have one brief one for Jackie. Since we are really looking at system issues, when you portrayed when viruses, the dates, those are the dates when they were defined or those are the dates when the person was sick? And so tell us a little bit more about how the system works and the lag between when somebody is sick and how that virus moves away to finally be defined.

DR. KATZ: Right. So, the dates that you will see against the viruses in the HI is the date the virus sample is collected. That is the information that comes with the virus. So, presumably, when the person was sick.

However, the virus first is sent to a National Influenza Center. And then they, depending on the Collaborating Center that they send their viruses to and the algorithm that they have for sending viruses, there may be some delay. It could be weeks. It could be months before the collaborating center actually receives the virus.

What we do here in the U.S. and I can only speak for the U.S. algorithm is starting in the beginning of October, we ask all public health state laboratories to send the first ten viruses that they receive in the season of a particular subtype. And then after that, to go to five, we also have contracting labs, who grow the viruses up for us. But we have a set algorithm and we tell them, don't delay once you have isolated the virus and determined it is H3, it is H1. Send it to us.

CHAIR DAUM: Dr. Levandowski, something that hasn't been said before.

DR. LEVANDOWSKI: It hasn't been said today but it has probably been said before.

(Laughter.)

DR. LEVANDOWSKI: For Dr. Katz, the nomenclature for naming the strains is the type A or B and then the place it came from and then the

accession number and then the year that it was isolated. So, what does that Swiss number means?

DR. KATZ: That means it was collected in 2013.

DR. LEVANDOWSKI: No, but I mean the nine million --

DR. KATZ: I'm sorry. I don't know. Some -- I don't think that they started from one.

CHAIR DAUM: One certainly hopes not. Okay, I think we are ready to vote. Any objections to that or any other comments? There is always someone. Dr. Hudgens.

DR. HUDGENS: Sorry. I would really like to hear directly from Dr. Grohskopf because I think when we vote on 1C here, it is going to be contrary to the data she showed us and I would just like to hear directly from her about that and the data she showed us on Yamagata.

CHAIR DAUM: So, before we start on 1A and 1b, Dr. Grohskopf, perhaps you could come to the microphone and comment on 1C, which is the inclusion of a B/Phuket-like virus, Yamagata lineage. Any microphone is fine. It is up to you.

Can we get the slide back up? That's been a challenge today.

DR. VIJH: If you can tell me the number.

DR. HUDGENS: I think it is slide six.

DR. GROHSKOPF: And if you could repeat the question, please.

DR. HUDGENS: My question is this. On slide six you showed this morning, 94 percent of the viruses characterized of the Yamagata lineage were of the Massachusetts type. And we are about to vote to switch the Yamagata strain from Massachusetts to something else. And that seems to be consistent with some of the other data we saw this morning but contrary to your data. And I would like to hear you comment on that. I'm talking about this slide and the bullet under Yamagata, where it says 94 percent of the viruses were Massachusetts-like. And we are about to vote to switch from Massachusetts to something else.

CHAIR DAUM: Thank you for your help, Dr. McInnes.

DR. GROHSKOPF: Thank you. I'm not a virologist. So, I am going to enlist the aid of Dr. Katz, where needed.

But as Dr. Katz explained earlier, I think this question came up earlier, although I might have misunderstood it at that time, these data are from the WHO and National Respiratory and Enteric Virus Surveillance System labs that are located in the U.S. and some of the territories, and I believe D.C. as well, and they are not representative of the global geographic picture, which was presented by Dr. Katz. So, I know that that is part of that answer.

Dr. Katz, is there anything else you would like to add to that?

DR. KATZ: No, thanks, Lisa. I think it just goes back to the comment I made earlier about for the CDC data, the B/Massachusetts antisera still covered the majority of viruses but we were seeing an increasing number of four-fold reductions. In other laboratories, they saw a bigger difference. Certainly, all the viruses have moved to the clade 3 viruses. Massachusetts is a clade 2 genetic group. And in other international laboratories, they saw bigger differences in their studies in their assays. And for at least the London group and the Australian group, they saw very poor coverage with antisera to B/Massachusetts. I think it was on the order of 20 or 30 percent. So, more like 70 percent low reactors.

DR. HUDGENS: Well, I think this committee is mostly interested in what is happening in the United States and not what is happening elsewhere.

CHAIR DAUM: Dr. Weir.

DR. WEIR: Just a question for Dr. Katz to help clarify this. Is it possible that certain areas of the world have more B/Yamagata activity than the United States?

DR. KATZ: Certainly, there were some areas that had more influenza B activity. I am just going back to the maps. And certainly, in Europe,

there was more activity and also more activity in Australia. So, in those areas, the WHO collaborating centers in those areas did find a bigger difference.

DR. WEIR: But isn't that one of the aspects of the recommendation to change a strain is the seeing where it is and the prevalence and how the circulation patterns are? In other words, I am assuming that you guys, when you were talking about this last week, must have felt that there was an increasing proportion of B/Yamagata strains that were more like B/Phuket than --

DR. KATZ: Definitely. Yes, definitely.

CHAIR DAUM: Thank you, Dr. Weir. Okay, with that, I think we are ready to vote.

I have some voting instructions here. I don't know how relevant they are. Let's assume they are. An electronic voting system in which the votes are cast simultaneously will be --

DR. LEVY: I'm really sorry to do this.

CHAIR DAUM: I'm sorry, too.

DR. LEVY: I'm not sure I understood the resolution of whether there is a conflict between the strains that are recommended based on the global distribution of the virus versus in the U.S. I'm not sure I understood the answer.

CHAIR DAUM: Perhaps Dr. Weir would like to comment on that.

DR. WEIR: No, that wasn't my point. We are making a decision for the U.S. but my point was that when they look at the strains in the WHO, when the decision is made, they are trying to look at the entire world. And a lot of times what you see occurring in one part of the world is predictive of what will then spread to the rest of the world. That is why you try to look at the entire picture and maybe just a single small area.

DR. KATZ: Sorry. I'm sorry.

CHAIR DAUM: No, not a problem. Dr. Katz, please.

DR. KATZ: Can I just remind people, too, that in the antigenic cartography that the viruses circulating globally, and this is as Dr. Weir has just said, we are really clustered in the group of viruses represented by B/Phuket. And that difference from the Massachusetts viruses was quite distinct.

CHAIR DAUM: More comments. Dr. Englund.

DR. ENGLUND: I just want to say that we are voting for the U.S. It is incredibly important to see what is going on in Asia and the southern hemisphere. That is why the U.S. government pays for all this surveillance or helps support all this surveillance because we know it drifts westward and northward.

So, if I can simplify my understand, so I think it is crucially important to see what is going on because in the past, some people have analyzed and there is a really high proportion that those viruses come to us next.

CHAIR DAUM: Thank you, Dr. Englund. Any other comments? Okay, then we will go to a vote.

The questions are on the screen. An electronic voting system is here, in which the votes are cast simultaneously will be used. While you are in the process of voting, the buttons will keep flashing, the button on the microphone. Please press "yes," "abstain," or "no," depending on your vote. While the vote is open, if you would like to change your vote, simply press a different button. This will change your vote for the record.

The buttons will keep flashing until voting is officially closed and your vote is locked in. The votes will be displayed on the TV screen. For the record, I will read the votes -- you will read the votes. Okay.

(Laughter.)

CHAIR DAUM: For the record, Dr. Vijh will read the votes. Thank you, Dr. Vijh.

So, let's go with the first question. For the composition of the trivalent 2015-2016 influenza virus vaccine in the U.S., does the committee

recommend inclusion of an A/California/07/2009 H1N1-like virus? So, you see the lights flashing in front of you. Please vote.

DR. VIJH: So, I'm going to read the votes for the record.

CHAIR DAUM: Dr. Edwards has left on an airplane.

DR. VIJH: Yes. So, it is Dr. Levandowski, yes; Dr. Englund, yes; Dr. Moore, yes; Dr. Lynfield, yes; Dr. Sawyer, yes; Dr. Hudgens, yes; Dr. Long, yes; Dr. Gellin, yes; Dr. Daum, yes; Dr. Piedra, yes; Dr. McInnes, yes; Dr. Bennink, yes; Mr. Raymond, yes; Dr. Stanek, yes; Dr. Levy, yes; and Dr. Wharton, yes. So, for the record, it is 16 votes yes, which is a unanimous vote.

CHAIR DAUM: Thank you very much, Dr. Vijh. And now we will go to the second question. For the composition of the trivalent 2015-2016 influenza vaccine virus -- sorry, I can read -- influenza virus vaccine in the U.S., does the committee recommend B, inclusion of an A/Switzerland -- here is that number -- 9715293/2013 H3N2-like virus. So, the little lights are flashing again and please vote.

Is that that pesky Dr. Edwards again?

DR. VIJH: Okay, so I am going to read the votes for question 1B. It is Dr. Levandowski, yes; Dr. Englund, yes; Dr. Moore, yes; Dr. Lynfield, yes; Dr. Sawyer, yes; Dr. Long, yes; Dr. Hudgens, yes; Dr. Gellin, yes; Dr. Piedra,

yes; Dr. McInnes, yes; Dr. Bennink, yes; Mr. Raymond, yes; Dr. Stanek, yes; Dr. Levy, yes; and Dr. Wharton, yes. So, again, it is 16 votes and a unanimous vote.

CHAIR DAUM: And now moving on. Question is 1C. For the composition of the trivalent 2015-2016 influenza virus vaccine in the U.S., does the committee recommend inclusion of a B/Phuket/3073/2013-like virus B/Yamagata lineage.

So, the lights are flashing once more. Please vote.

DR. VIJH: So I am going to read the votes for question 1C. It is Dr. Levandowski, yes; Dr. Englund, yes; Dr. Moore, yes; Dr. Lynfield, yes; Dr. Sawyer, yes; Dr. Hudgens, no; Dr. Long, yes; Dr. Gellin, yes; Dr. Daum, yes; Dr. Piedra, yes; Dr. McInnes, yes; Dr. Bennink, yes; Dr. Raymond, yes -- Mr. Raymond, yes; Dr. Stanek, yes; Dr. Levy, yes; Dr. Wharton, yes. And it is 15 votes yes and one vote no, for the record.

CHAIR DAUM: Thank you very much, committee members. And for our final question is regarding the quadrivalent vaccine for those companies that manufacture a quadrivalent vaccine. For the quadrivalent 2015-2016 influenza vaccine in the U.S., does the committee -- bless you -- does the committee recommend inclusion of a B/Brisbane/60/2008-like virus B/Victoria lineage as the second influenza B strain in the vaccine?

So, here your lights are flashing again and there is an opportunity to vote.

DR. VIJH: So I am going to read the votes for the record for question 2A. It is Dr. Levandowski, yes; Dr. Englund, yes; Dr. Moore, yes; Dr. Lynfield, yes; Dr. Sawyer, yes; Dr. Hudgens, yes; Dr. Long, yes; Dr. Gellin, yes; Dr. Daum, yes; Dr. Piedra, yes; Dr. McInnes, yes; Dr. Bennink, yes; Mr. Raymond, yes; Dr. Stanek, yes; Dr. Levy, yes; and Dr. Wharton, yes. So, it is a unanimous vote of 16 yes.

CHAIR DAUM: Thank you very much, Dr. Vijh.

I would like to close the meeting. Are there any final comments that anyone would like to make before I do so? Then, I will consider this meeting adjourned.

Our next meeting is in May and the topic is Ebola vaccine.

DR. VIJH: We don't know the date yet. It is being planned.

CHAIR DAUM: Dr. Vijh will communicate with you. Thank you very much, committee members, for your diligence.

(Whereupon, the above-entitled matter went off the record at 2:03 p.m.)