FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
Vaccines and Related Biological Products Advisory Committee
155th Meeting

OPEN PUBLIC MEETING

FDA White Oak Campus
Great Room Salon B&C
Silver Spring, MD 20903

March 6, 2019

PARTICIPANTS

Hana El Sahly, M.D.	Baylor College of Medicine
Arnold Monto, M.D.	University of Michigan
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine
Sheldon Toubman, J.D.	New Haven Legal Assistance Association
Melinda Wharton, M.D., M.P.H.	National Center for Immunization and Respiratory Disease
Leonard Friedland, M.D.	GlaxoSmithKline
Myron Levine, M.D., D.T.P.H., F.A.A.P.	University of Maryland
Serina A. Hunter-Thomas, M.S.A., R.N.	Food and Drug Administration (FDA)
Geeta K. Swamy, M.D.	Duke University
Jerry P. Weir, Ph.D.	Food and Drug Administration (FDA)
Philip Krause, M.D.	Food and Drug Administration (FDA)
Konstantin Chumakov, Ph.D.	Food and Drug Administration (FDA
Marion Gruber, Ph.D.	Food and Drug Administration (FDA)
Robin Levis, Ph.D.	Food and Drug Administration (FDA)
Carolyn Wilson, Ph.D.	Food and Drug Administration (FDA)
Keith Peden, Ph.D.	Food and Drug Administration (FDA)
Prabhakara Atreya, Ph.D.	Food and Drug Administration (FDA)
Celia Witten, PhD, M.D.	Food and Drug Administration (FDA)
Peter Marks, PhD, M.D.	Food and Drug Administration (FDA)

TABLE OF CONTENTS

CALL TO ORDER/INTRODUCTIONS

DR. EL SAHLY: Good morning, everyone. It's 8:05. I would like to get started.

Well, I want to welcome all of you to the 155th meeting of the Vaccines and Related Biological Products Advisory Committee on this very cold March morning. I want to welcome the people in the room, as well as the individuals dialing in via the webcast. We will begin by introducing the committee members. Each member to introduce themselves, their institutional affiliation, and expertise.

I'll begin here: Hana El Sahly, Baylor College of Medicine, Adult ID and Clinical Vaccine Development.

DR. SWAMY: Good morning. Geeta Swamy. I'm an OB-GYN faculty member at Duke University and work in maternal immunization.

DR. WHARTON: Melinda Wharton from the Immunization Services Division at the Centers for Disease Control and Prevention. I'm an adult infectious disease specialist.

DR. BENNINK: Jack Bennink, NIAID, National Institutes of Health. I'm a viral immunologist.

DR. EDWARDS: Kathy Edwards. I'm a professor of pediatrics at Vanderbilt University and work on vaccines.

DR. WIESEN: Andrew Wiesen, preventive medicine physician. I work for the Department of Defense, Assistant Secretary of Defense for Health Affairs.

DR. KATZ: Jackie Katz, deputy director of the Influenza Division at CDC and director of the WHO Collaborating Center in Atlanta at CDC.

DR. NOLTE: I'm Hendrik Nolte, industry rep. I'm a pulmonologist and also trained as an allergist. Senior VP for research at ALK.

DR. GRUBER: Good morning. My name is Marion Gruber and I'm the director of the Office of Vaccines Research and Review at CBER.

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

DR. SHANE: Good morning. I'm Andi Shane.

I'm from Emory University in Atlanta, and I'm a pediatric infectious disease physician.

DR. OFFIT: Paul Offit, Children's Hospital of Philadelphia, pediatric infectious diseases.

DR. MONTO: Arnold Monto, University of Michigan, infectious disease epidemiology.

DR. LEVINE: Mike Levine.

DR. MEISSNER: Jumping right over me.

DR. LEVINE: Sorry.

DR. MEISSNER: You're pretty quick. Cody Meissner, professor of pediatrics at Tufts University and a pediatric infectious disease specialist.

DR. LEVINE: Good morning, everyone. Mike Levine. I'm the associate dean for Global Health Vaccinology and Infectious Diseases at the University of Maryland School of Medicine.

DR. KURILLA: Mike Kurilla, director of the Division of Clinical Innovations, at the National Center for Advancing Translational Science within NIH, a pathologist by training and vaccine development.

DR. JANES: I'm Holly Janes. I'm at the Fred

Hutchinson Cancer Research Center, and I work in vaccine evaluation clinical trial design. My specialty is biostatistics.

DR. EL SAHLY: Thank you. Welcome to all. Now Serina is going to read some housekeeping and Conflict of Interest statement.

ADMIN ANNOUNCEMENTS, COI STATEMENT

MS. HUNTER-THOMAS: Thank you, Dr. El Sahly. Welcome, everyone. My name is Captain Serina Hunter-Thomas. It is my pleasure to serve as the Designated Federal Officer for this meeting.

I would like to mention some brief housekeeping items before we begin with the Conflict of Interest statement. First, as we're deliberating through the day, if everyone can speak into the microphone, first stating your name, so that we can have an accurate record of this meeting and the names and comments.

Secondly, if you have any cell phones, please put them on silent or mute. And also, there is representation here from the press in the back. If the

press could stand up so that everyone can identify you. Is Paul here or Megan? Hi, Paul. Thank you for coming. And then we do have a transcriptionist here. Her name is Linda Giles. Thank you, Linda.

I will go ahead and proceed with the Conflict of Interest statement.

The Food and Drug Administration is convening today, March 6, 2019, for the 155th Meeting of the Vaccines and Related Biological Products Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972. Dr. Hana El Sahly is serving as Chair of the meeting for both topic one and topic two today. The meeting will have two separate Conflict of Interest disclosure statements read prior to each topic session that will occur during the meeting today. This Conflict of Interest statement will be available for public viewing at the registration table.

Today, on March 6, 2019, for topic one, VRBPAC will meet in open session to discuss and make recommendations on the selection of strains to be included in an influenza virus vaccine for the 2019

Northern Hemisphere influenza season. This topic is determined to be a Particular Matter Involving Specific Parties or PMISP.

In the afternoon for topic two in the open session, the committee will hear overview presentations on the intramural laboratory research programs of the Laboratory of Amino Regulation and the Laboratory of Retroviruses. Per agency guidance, this session is determined to be a non-particular matter, which would have no impact on outside financial interests. Hence, no effective firms were identified, and members were not screened for this topic.

In the latter part of the afternoon, the meeting will be closed to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy, per 5 U.S. Code 552(b)(c)(6). Related to the discussions at this meeting, all members and SGE consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or

minor children, and for the purpose of 18 U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, speaking, teaching, writing, patents and royalties, and primary employment.

The FDA has determined that all members of this advisory committee are in compliance with Federal Ethics and Conflict of Interest laws. Under 18 U.S. Code 208, Congress has authorized the FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Hendrik Nolte is currently serving as the acting industry representative for this committee. Dr. Nolte is employed by ALK, Inc. and industry representatives act on behalf of all related industry

and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Hence, industry representatives are not screened and do not participate in the closed session and do not have voting privileges.

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

Dr. Jacqueline Katz is employed by the Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases. She is an internationally known expert in influenza virus epidemiology, worldwide influenza disease burden, and influenza virus vaccines. Dr. Katz is a regular government employee and serves as the speaker for this meeting under topic one. She is also serving as a

temporary non-voting member for topic one.

Dr. Lisa Grohskopf is employed by the Centers for Disease Control and Prevention, influenza division. Dr. Grohskopf is a subject matter expert on influenza epidemiology and influenza viral vaccines. She is serving as a speaker at this meeting.

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

The FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms, its products, and, if known, its direct competitors. We would like to remind members, consultants, and participants that if

the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from such involvement and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest statement for the public record. I would like to hand the meeting back over to Dr. El Sahly. Thank you.

INTRODUCTION

DR. EL SAHLY: Thank you, Serina. Anissa Cheung, who is the regulatory coordinator from the Division of Viral Product at the FDA, will now introduce the meeting. Anissa.

MS. CHEUNG: Good morning. I'm going to introduce the discussions, topics for today, which is the influenza virus vaccines for the 2019/20 strain selections.

So the purpose of today's VRBPAC discussions is to review the influenza surveillance and

epidemiology data, genetics, and antigenic characteristics of the recent virus isolates, serological responses to current vaccines, and the availability of the candidate vaccine strains and also reagents. At the end of the review of this data, the committee will be asked to make recommendations for the strains of influenza A(H1N1) and the B viruses to be included in the 2019 and '20 influenza vaccine license for use in the United States. Please note that today we are not going to make recommendations for the H3N2 strains. And the details for the delayed recommendations of the H3N2 strain will be discussed in Dr. Katz's presentation.

So you will hear some presentations on the types of analysis used for vaccine strain selections and this includes the epidemiologies of circulating strains. CDC will give a talk on the surveillance data from both the U.S. as well as around the world. You will also hear talk on the antigenic relationships amongst the contemporary viruses and the candidate vaccine virus. The types of methods and also the

techniques you will be hearing about include the hemagglutinations inhibitions tests using the post-infection ferret sera, as well as the hemagglutination inhibition tests using panels of sera from humans receiving recent inactivated influenza vaccines.

You will also hear some results from the virus neutralization test, antigenic cartography, as well as the phylogenetic analysis of the HA and the NA genes of the recently circulating virus, and also the candidate vaccine virus. You will also hear some reports on vaccines' effectiveness, and those talks will be given by CDC and the Department of Defense.

There are always challenges for vaccine strain selections. First, the vaccine effectiveness depends on the match between the hemagglutinin of the vaccines and also the hemagglutinins of the circulating strains of viruses. And there is antigenic drift of HA continuous for both the influenza A and B strains, but the antibody of HA correlated with the vaccine's efficacies.

Another challenge is the timeline for

influenza vaccine productions is relatively fixed. Normally, we will have the strain selections occur in late February or early March so that the vaccines will be available for the Northern Hemisphere, the winter influenza seasons. And you may know that the manufacturer typically begins production of the monovalent of one of the strains at risk so that they will meet the timeline.

Now the challenge is the availability of the reference strain, which we also call them the candidate vaccine virus that needs to be suitable for vaccines manufactured. The vaccine yield depends greatly on the growth property of the strain used for manufacture. Also, the strain-specific reagent is required for potency determinations for the formulations of both the inactivated and the recombinant protein vaccines.

This is just an illustration to show you the rigidity of the seasonal influenza vaccine's productions timeframe. As I mentioned, normally, we have the strain selections in late February to early March, and after that there are overlapping activities

that include the generation of the reference virus and also productions of the reference reagent for the potency determinations, as well as the production of the vaccine drug substance and drug product. These activities take around five to six months after the strain selections in order to get the vaccines ready prior to the influenza season.

So the working virus seed for the production of the inactivated influenza vaccines are traditionally egg-isolated candidate vaccine virus, and the antigenicity is characterized by the WHO CC. Starting in August 2016, the use of the MDCK cell isolated candidate vaccine virus strain was approved for the manufacture of MDCK cell based influenza vaccine Flucelvax monovalent bulk. And these cell based candidate vaccine viruses, they are manufacturer specific, and they are derived from two approved WHO CCs. The antigenic analyses follow the same way that we assess for the egg isolated vaccine virus strain. All the working virus seeds are approved for quality and safety by the National Regulatory Authority.

There are two antigenically distinct lineages of influenza B that are co-circulating and are represented by B/Victoria and B/Yamagata lineages. Currently, both trivalent and quadrivalent influenza vaccines are available in the U.S. There are eight quadrivalent vaccines licensed in the U.S.; and according to the 2018 and '19 data, more than 80 percent of the influenza vaccines are quadrivalent.

The current process for selecting appropriate B strains for inclusion in the trivalent and quadrivalent vaccines is similar to what we used for the trivalent vaccine's recommendations. The WHO and the VRBPAC will review the data and then make recommendations for each formulation.

So let me recap what we had recommended under the influenza vaccine compositions for the 2018 and '19. So, about a year ago, the same committee, VRBPAC, met on March 1, 2018, to make recommendations for the antigenic compositions of the 2018 to 2019 influenza virus vaccines in the U.S. The committee recommended A/Michigan/45/2015(H1N1)pdm09-like virus and

A/Singapore/INFIMH-16-0019/2016(H3N2)-like virus for the two B strains. For trivalent, they recommended a B/Colorado/06/2017-like virus which is a Victoria lineage; for quadrivalent vaccines containing the above three viruses and also a B/Phuket/3073/2013-like virus from the Yamagata lineage.

In the same year, the VRBPAC also met on October 3, 2018, to make recommendations for the antigenic compositions on influenza virus vaccines for the Southern Hemisphere 2019. And the committee recommended A/Michigan/45/2015(H1N1)pdm09-like virus, a A/Switzerland/8060/2017(H3N2)-like virus, a B/Colorado/06/2017-like virus from the Victoria lineage. For quadrivalent vaccines, they also include a B/Phuket/3073/2013-like virus from the Yamagata lineage.

So, this year, on February 21, 2019, the WHO made recommendations for influenza vaccine compositions for the Northern Hemisphere 2019 and '20. The WHO recommended the following viruses used for the trivalent influenza vaccines in the 2019 and '20

Northern Hemisphere influenza seasons: an A/Brisbane/02/2018(H1N1)pdm09-like virus. They recommended to make a change from last year's recommendations A/Michigan/45/2015. For the B strain, they recommended a B/Colorado/06/2017-like virus from a Victoria lineage, which has no change from the 2018 and '19 recommendations. For the H3N2 strain, the recommendations will be announced on the 21st of March 2019.

So, they also recommended the quadrivalent vaccines, which is supposed to contain two influenza B viruses, will contain the above virus and also a B/Phuket/3073/2013-like virus, which is from the B/Yamagata lineage. And there is no change from the 2018 and '19 Northern Hemisphere recommendations. As in the previous years, the national or the regional control authority approved the composition and the formulation of vaccines used in each country.

So, this is the role of this committee. At the end of the discussions and after the review of all the data, the committee will be asked to make

recommendations for the influenza strain that should be included for the antigenic compositions for the 2019 and '20 influenza virus vaccines in the U.S.

So I would like to give you the options for the strain compositions for the 2019 and '20 trivalent influenza vaccines.

For the influenza A(H1N1), you can either recommend an A/Brisbane/02/2018(H1N1)pdm09-like virus or recommend an alternative H1N1 candidate vaccine virus.

For influenza A, the H3N2 strain, the recommendations will be finalized on March 22, 2019.

For the influenza B strain included in the trivalent vaccines, you can either recommend a B/Colorado/06/2017-like virus, which is from the Victoria lineage, or recommend an alternative candidate vaccine virus from the B lineage, or you can recommend a candidate vaccine virus from the B/Yamagata lineage.

So these are the options for strain selections for the second influenza B strain in a quadrivalent influenza vaccine. So you can either recommend

inclusion of B/Phuket/3073/2013-like virus from the 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.

So, before I end my presentation, I would like to fresh up the questions that you may ask to be voted at the end of the discussions for today. Thank you.

DR. EL SAHLY: Thank you, Anissa. Do we have any questions for Anissa? All right. Thank you.

U.S. SURVEILLANCE

DR. EL SAHLY: Next, I want to welcome Dr. Lisa Grohskopf, the associate chief for policy and liaison at the Activities, Epidemiology and Prevention branch for influenza at the CDC. Dr. Grohskopf is going to review the U.S. surveillance data.

DR. GROHSKOPF: Thanks. Good morning, everybody. So this will be an overview of the 2018/19 surveillance data as it exists so far this season and also a little bit on the preliminary VE estimates from the Flu VE Network for 2018/19.

So first U.S. influenza surveillance.

Starting with virologic surveillance. These are data that come from the WHO Collaborating Laboratories and National Respiratory and Enteric Virus Surveillance System laboratories that report weekly to CDC. These include approximately 300 clinical laboratories and approximately 100 public health laboratories.

Those data are represented separately on the two charts on this slide. The clinical laboratories, by and large, don't generally subtype out A virus or perform lineage determination on the B viruses. So we have a few fewer colors in the graph on the left. The A's are in yellow and the B's are in green. Calendar week is on the x-axis and the line represents the percent of specimens positive. The bars represent numbers of the different subtypes.

So you can see from the clinical laboratories, we have an overwhelming preponderance of the influenza A viruses throughout the course of the season. Turning to -- whoops, not sure what I did there. Sorry about that. Okay. Turning to the public health laboratory chart, by and large, these labs do subtype out A

viruses and do lineage determinations on Bs.

We have (H1N1)pdm09s in orange and the H3N2s in red. And this slide gives us an opportunity to talk about some of the things that have been interesting about this season, which are that, for one thing, we haven't seen very much in the way of B yet. You can see there's not much green here. And for another, the A's have been interesting in that nationally, if you look at the whole country for the whole course of the season thus far, H1N1s have predominated.

But from early on in the southeast of the United States, region four H3N2s were actually in high numbers and predominating. And then, last week, this data that I'm presenting you today is from the most recent FluView, which is for the calendar week 8 which ended February 23. That week -- I'm not talking for the whole span of the season, but for just that week -- for the first time, the H3s outnumbered the H1s in this data. So we've had a little bit of a shift there.

Next, some indices of influenza-like illness. This data comes from ILINet, which is a network of

approximately 3,500 outpatient facilities who report weekly on the percent of outpatient visits that are for ILI.

So, in the graph on the left, this is data over the cross of seasons. Each line represents a different season. Our current 2018/19 season is in the red line with the superimposed red triangles. Calendar week again is on the x-axis. What you see here is that we are above the baseline, which is calculated based on influenza ILI activity during non-influenza season periods during the year. We are above baseline. We're at five percent for Week 8, similar to what it was for Week 7, also five percent.

Just to put things into context, the peak percent of visits that were for ILI in recent previous seasons ranged from about 3.6 percent in the 2015/16 season to 7.5 percent last season, which was a relatively severe season, as most of you are familiar with.

The ILINet data can be used to make estimates by state of ILI activity. So this is in the graph on

the -- or the figure, rather, on the right. This is a map that shows ILI activity by state. This is just a snapshot for Week 8. The change from Week 8 over Week 7 was that during Week 7 there were 30 states plus New York City recording high activity, and then for Week 8, we had 33. So an increase of three states, plus New York City still there.

Moving on to hospitalizations, these are data from FluSurv-NET. These are laboratory-confirmed influenza hospitalizations coming from this network. The data are cumulative, so we expect that the lines are going to go up over the course of time. Calendar week, again, on the x-axis. The different lines represent the hospitalization rate per 100,000 population. There's one line for overall and then there's a line -- a separate line for various of the age groups that you can see in the legend.

The overall rate as of Week 8 is 32.1 per 100,000. Just for comparison, for last season 2017/18, Week 8, the cumulative rate was 84 per 100,000, so 84 versus 32 per 100,000.

Just moving back again to the current season, the highest rates are, as is not atypical, among those aged 65 and older at 91.5 per 100,000, followed by children under 5 years of age at 45.5 per 100,000.

Next, mortality indices. So we have two here: one is the pneumonia and influenza mortality from the NCHS Mortality Surveillance System. These data are not lab-confirmed influenza deaths, but are deaths that come – death records, basically, that come from death certificate data. These tend to be in somewhat of a flux over the course of the year as more data are gathered from death certificates and things are ascertained with a bit more certainty.

At the moment, we have for Week 8, 7.1 percent of deaths reported in this network were due to pneumonia and influenza diagnoses. That's a little bit below the baseline of 7.3. You can see in the previous week we did peak a little bit above baseline and are back down. For comparison with other seasons, if you examine the range of weeks for which the percent of deaths being due to P&I were above the baseline. Those

ranged from 4 weeks in 2015/16 to 16 weeks in '17/'18.

On the right-hand side, we have the influenza-associated pediatric deaths. Deaths of children under the age of 18 associated with lab-confirmed flu have been a reportable condition in the United States since 2004. We have a number of seasons represented on this slide from 2015/16 through to the current 2018/19 season. As of the Week 8 data, there were 56 deaths recorded for this season, of which 15 were reported during Week 8. Among the 15 reported during Week 8, eight were (H1N1)pdm09, one H3N2, and six unsubtyped.

This is the last surveillance slide, and this gets a little bit at genetic diversity. I'm not going to spend a lot of time on this because it's going to be covered in more detail in Dr Katz's presentation. In the main pie chart on the left, that sort of reflects the entire population of viruses that were characterized at CDC. You can see the A's predominate, the unsubtypes are in yellow, (H1N1)pdm09 in orange, and H3N2 in red.

Just to draw some attention to the H3N2 viruses, which in that set of four pie charts is the one in the upper left, there's a predominance in that graph of 3C.3a. Among the H3N2s in general, there's considerable diversity with multiple clades and subclades circulating. And the proportion and spread of the 3C.3a's has been increasing in recent weeks.

So, in summary, influenza activity remains elevated in the U.S. for this season. Influenza A(H1N1)pdm09 viruses have predominated overall for the whole U.S., but H3N2 viruses were detected more commonly than H1N1 viruses in the southeast and during Week 8 predominated nationally. An increasing proportion of the H3N2 viruses belong to the 3C.3a genetic group, which is antigenically distinct from the 3C.2a genetic group. And, of course, as mentioned earlier, we're seeing, so far, very low proportions of influenza B viruses this season.

So moving on to a little bit about the interim 2018/19 VE estimates. These come from the U.S. Flu VE Network. This map just points out where the sites that

participated in the network are. There are five. We have Kaiser Permanente Washington, Baylor Scott and White in Texas, Marshfield Clinic Research Institute in Wisconsin, the University of Michigan, and the University of Pittsburgh in Pennsylvania.

A brief bit on methods. Enrollees are outpatients, aged 6 months or older with acute respiratory illness with cough for no more than seven days. Dates of enrollment for the data that I'm going to present are November 23, 2018, through February 2, 2019. The design is a test-negative case-controlled design, which involves comparing vaccination odds among the influenza RT-PCR positive cases with the RT-PCR negative controls.

So everybody enrolled presents with acute respiratory illness and everybody is tested. Those that are test-positive are classified as cases; those who are negative are classified as controls.

Vaccination status is defined as receipt of at least one dose of any 2018/19 seasonal influenza vaccine according to medical records, immunization

registries, and/or self-report. The data presented here were adjusted for study site, age, self-rated general health status, race, ethnicity, interval from onset of symptoms of illness to enrollment, and calendar time.

So results: Again, these are preliminary. The season's still ongoing, and we look forward to future data as more come in. In total, 3,254 were enrolled as of February 2 at the 5 sites. 465 or 14 percent were RT-PCR positive for influenza. 2,789 or 86 percent were negative. Looking at the 465 positives, we have another pie chart which examines the makeup of that group. The majority is more or less -- is very similar actually to the graph that we looked in U.S. surveillance. The majority of the viruses represented for (H1N1)pdm09, but we do also have some H3N2 in red. It's difficult to see the way this slide displays but Bs are, again, in the minority; B/Victorian and B/Yamagata each represent about one percent.

This graph summarizes the number of enrolled

participants and also the percent positive specimens and the number of positive and negative by week. You can see that the black line, which shows the percent positive, had a bit of an uptick during the latter half of January and continued to rise during February. The cutoff date for the folks in this analysis is where that dotted line is and so it includes through Week 5. Week 7 data at this point are incomplete because it basically only includes those who have completed test results. So these are data that, of course, will be updated as we get more and information is more completely ascertained.

So I have two results slides. This first one is interim adjusted VE against medically attended influenza; this time for all flu A and B for the season thus far in this analysis. I want to mention one thing. It's overall data for all age groups, and then we have some age categories. Normally, we try with the age categories to have a separate category for age 65 and older; but based on the numbers that we currently have for this analysis, there are just not enough to do

that. So, the oldest age category here is 50 and older.

Overall, the VE was 47 percent and statistically significant. We also see significant protection for 6 months through 17 years at 61 percent, and 18 through 49 years at 37 percent. The VE estimate for 50 and older is 24 percent and is not statistically significant.

We have data here, broken down by subtype; although, we're able to break that further down by age only for the (H1N1)pdm09. And for influenza A(H3N2), because the numbers are smaller, we only have an overall figure. So for (H1N1)pdm09, we have an overall VE for all ages of 46 percent. By age group: 6 months through 17 years, 62 percent; 18 through 49 years, 45 percent. The figure for 50 years and older is 8 percent and that estimate is not statistically significant. For influenza A(H3N2), we have an overall VE of 44, which is statistically significant.

In summary, interim results for 2018/19 season through February 2 indicate protection against

influenza, with a VE of 47 percent against any influenza virus; 46 percent against (H1N1)pdm09; and 44 percent against H3N2.

Effectiveness estimates among children aged 6 months through 17 years are 61 percent against any flu and 62 percent against pdm09. The effectiveness estimates vary between 37 percent and 45 percent among adults aged 18 through 49 years. Effective estimates are not statistically significant among those greater than 50 years. These data, again, are preliminary and we look forward to seeing more results as the season progresses. And the U.S. Flu VE study will continue enrolling through the end of the season.

I want to thank all my colleagues who work really hard to get all these data together every week; in particular, Lynnette Brammer and Brendan Flannery who presented on these topics at the ACIP meeting last week and who provided these slides. Thanks.

DR. EL SAHLY: Thank you, Dr. Grohskopf. Dr. Edwards.

DR. EDWARDS: Thank you very much, Lisa. This

is very, very helpful. I think I already know the answer to this question, but I thought I should probably ask it anyway. Do you see, within this network, that there is going to be an ability to look at both cell-based and egg-based vaccines, or have you looked sort of at distribution of a vaccine receipt?

DR. GROHSKOPF: Up till now, it's been difficult to do that. I'm not really sure if it's going to be possible this season yet. We've been fortunate that as time has gone on, it's becoming increasingly possible to do that. There was a time when they couldn't look at LAIV separately and then they were able to. So I don't know for certain what's going to happen this season though, yet.

DR. EL SAHLY: Dr. Bennink.

DR. BENNINK: Although the data's limited at this stage and things, could you comment on the difference in VE between some of the Canadian data that came in? Even though we have three of the five sites are up in the north and we don't -- in some ways in the VE, it would be nice to have because you're making a

comment about the southeast and stuff. It would be nice to have something down in the southeast or in the southwest or something like that. But can you comment on the -- there's quite a difference in VE and the early data between what the Canadians have seen and what we're seeing in the U.S.

DR. GROHSKOPF: Yes, good point. This is something we've seen in previous seasons as well and it's difficult to know for certain. We do know, as it was very well illustrated this season, that sometimes regionally, we see a big difference in what's circulating. So, that could possibly feed into it. There may be differences in coverage and for some estimates and in the Canadian literature, the sample sizes tend to be even smaller. So we also have the issue of uncertainty of the precision of the estimates.

It's possible in some in some situations where the competence intervals are wider, that maybe they're not as different as they look. Because, you know, we may be looking at data that gives a point estimate, but the confidence interval around that's actually fairly

large. I don't really have any idea about potential regional differences in VE in our network. Unfortunately, we only have the five sites. Although, that would be interesting to know.

DR. EL SAHLY: Dr. Kurilla?

DR. KURILLA: Has there been any data regarding the time dependence of vaccination? I'm wondering, particularly with regard to the older populations, are we being too aggressive in vaccinating them so early that their protection is actually dropping off by the time flu season arrives?

DR. GROHSKOPF: That hasn't been examined specifically with this data for this season. There is a growing body of literature on waning of immunity. Some of it looks at antibody levels at decline. Some of it looks at declines in vaccine efficacy or effectiveness over time.

It does appear, at least from literature as it stands now, that that may be more of a pronouncing to happen among older adults than among younger people. And also, it may be more common with H3s than with H1s.

It's, definitely, an important point to consider.

One other thing to consider, though, is that there might not be a very solid understanding yet about what the potential negative consequences of waiting are in terms of, you know, what happens if the season is earlier than we expect? Or what happens if individuals are not returning to be vaccinated or get vaccinated late? So it's a very complicated issue, but an important one.

DR. EL SAHLY: Dr. Meissner and then Dr. Monto. Sorry.

DR. MEISSNER: Thank you. And I just wanted to follow up on Kathy's question about VE between egg-based and cell-culture grown. Similar question as it relates to the high-dose influenza vaccine and adjuvant in -- you think it will be possible to get any effectiveness data this year?

DR. GROHSKOPF: I don't want to say anything until the team finally has a solid sense of that. It might be conceivably possible with high dose. I'm not sure about adjuvant. A lot depends on how much is the

uptake of the different vaccines at the different sites. And I don't know completely for certain at this point, but I do know that's something that's being worked on.

DR. EL SAHLY: Dr. Monto.

DR. MONTO: I think, as an insider on this, that we should realize that these are really preliminary estimates. The season started relatively late. And this was really pushing it to come up with estimates. So the confidence intervals are large, but it's interesting that the -- just as in past years with H1N1, we saw much better effectiveness in the young and then older individuals. This has been dramatic in the past.

In terms of what to expect in the future, one of our sites is actually using a lot of recombinant vaccine this year. So, it is possible, given controlling for site differences, that you might see something there. And there are efforts to look at high dose, and this is not easy, given that this is an observational study and choices are made about who gets

the vaccine.

DR. EL SAHLY: Okay. Dr. Grohskopf, how much of the data regarding receipt of vaccine is self-report and how much is it review of records?

DR. GROHSKOPF: Normally by this time -- it varies somewhat depending on the site. Normally, by this time some of it is still self-report. That becomes increasingly well characterized by the time the final estimates are reported. But the degree to which self-report is included, it varies on the site. I believe that's in the minority, at least right now. But everything gets confirmed by the time the final estimates are reported out in the late summer or fall.

DR. EL SAHLY: And any idea regarding vaccine usage and coverage nationwide, meaning is there any difference in coverage between this year and last year or is it too early to tell as well?

DR. GROHSKOPF: I think too early to tell that unless some -- Dr. Wharton may have something to say, though.

DR. WHARTON: So we did publish early season

coverage estimates in November. For children 6 months to 17 years of age, the estimated coverage was about 46 percent, which was about 7 percent higher than the comparable time during the previous season. And for those 18 years of age and older, that estimate was about 45 percent, which was about 6 percent higher than the comparable estimate last year. That doesn't mean that's where we'll be at the end of the season, but that's where we were in mid-November.

DR. EL SAHLY: Okay. Thank you. Additional questions? All right. Thank you, Dr. Grohskopf.

DR. GROHSKOPF: Thank you.

WORLD SURVEILLANCE/VIRUS CHARACTERIZATION

DR. EL SAHLY: Next, I will welcome Dr. Jacqueline Katz. Dr. Jacqueline Katz is deputy director influenza division and director of the WHO Collaborating Center for Surveillance Epidemiology and Control of Influenza, National Center for Immunization and Respiratory Diseases at the CDC as well. Dr. Katz.

DR. KATZ: Okay. Thank you. So we heard from Dr. Grohskopf just now, the current status of

surveillance and the preliminary biologic data for the U.S. I'm going to be presenting the global picture.

So, essentially, I'll be presenting a representative data set that was also presented at the information meeting in Beijing, after the vaccine consultation meeting, which was held from February 18 to the 20th. It was co-chaired by Dr. Dayan Wang, who is the director of the China National Influenza Center and representing the Beijing Collaborating Center and myself. And we had over 30 observers from different national influenza centers, reference laboratories, and ERLs, academia, and the veterinary sector. And as you know, the Global Influenza Surveillance and Response System is a network, coordinated by WHO of over 140 laboratories in over 100 countries. Well, I'll get the hang of this in a minute. Okay.

So this is just a snapshot of where we were. If you look at the left of this image, you'll see this is where we were this time last year. So we were on the downward slope of a very intense Northern Hemisphere season. In orange are influenza B viruses,

so you can see that they were quite prevalent late in the season.

And by comparison, if you look at the base there in the pale blue, that's the (H1N1)pdm09, which was fairly modest circulation last year. And on the right-hand side, you see the current season; the global circulation primarily in the Northern Hemisphere, where H1N1 is predominating overall. But there is some H3N2 activity in some countries in Europe, where H3N2 is predominating, as well as in Asia and Northern Africa, but it's more focal circulation.

This is showing the number of total specimens that came into the GISRS network. The black line is the tail end of the 2018 season, so the start of our Northern Hemisphere season. And the red line is the current 2019 first few weeks. So you can see overall that the numbers of specimens weren't as high as in the previous '17/'18 Northern Hemisphere season.

This shows just the percentage of viruses overall. Again, influenza A viruses vastly predominated about 95 percent of viruses with flu A

with a very small proportion being influenza B. And amongst the influenza A viruses, (H1N1)pdm09 viruses predominated globally.

So I'll turn now and talk about the (H1N1)pdm09 viruses specifically. And this map again from -- it's an activity map of the degree of outbreaks that WHO characterizes as local, regional, or widespread. And you can see the darker the red, the more widespread the activities. So a lot of activity in North America, in Asia, in some countries in Western Europe, and also in Russia.

These are the number of (H1N1)pdm09 viruses that were actually characterized antigenically at the collaborating centers. If you'll just focus on the green bars, that's the most recent reporting period that we'll be talking about today from September 2018 onwards. You can you can see that some of the collaborating centers, particularly the one in China, and VIDRL, which is the one in Melbourne, Australia, we're seeing an increase in the number of (H1N1)pdm09 viruses. This was a little unusual for Australia, but

they were reporting outbreaks of (H1N1)pdm09 in their summer months. So this was quite unusual and inter-seasonal activity.

So starting with the genetics of the viruses, this is a phylogenetic tree of the (H1N1)pdm09 hemagglutinin. This is over 2,000 sequences that's available in the GISAID database of viruses available since September. And you'll see at the base there highlighted in red is the Michigan/45/2015. That's the current component, H1N1 component, of our vaccine this season. And you can see since that time, since the recommendation in 2017 for the Michigan/45, just about all of the 6B.1 viruses and that's the majority of what is still circulating the 6B.1 clade. However, these viruses have acquired multiple substitutions there in the hemagglutinin. 74R and 164T are in antigenic sites. And these three substitutions have pretty much swept through the entire 6B.1 group. And so the collaborating centers felt it was appropriate now to designate this as a 6B.1A subclade.

So in addition to these changes, which

happened some time ago, more recently the majority of viruses now also contain a new substitution of S183P and this is right next to an antigenic site SB. And it's interesting that it's occurring independently in different parts of the tree, suggesting that there is some advantage for the viruses to acquire this substitution.

This is another tree developed by our colleagues at Cambridge University. And what I want you to focus on here is just every color and every bar represents a virus. So the colors of the color coding of the geographic region's shown at the bottom there. And really just the idea is that while a lot of viruses have hemagglutinins that have acquired this 183P, there's a lot of genetic diversity in the HA and multiple clusters forming. And so there's no one cluster with additional amino acids that is predominating or seems to be on the upward trend and taking over at this time.

And this is just, again, reiterating that the substitution of proline at 183 is now in about 84

percent of the (H1N1)pdm09 viruses circulating globally and that's happening across all of the regions.

Also, this is now a phylogenetic tree of the neuraminidase. Again, this is all available sequence data, so it's quite a busy tree. You can see again that there's quite a bit of diversity that is accompanying the diversity seen in the hemagglutinin.

So turning now to the antigenic characterization for the (H1N1)pdm09 viruses, as you heard earlier the traditional way we do this antigenic characterization is to perform a hemagglutination inhibition assay using host infection ferret antisera. Ferret antisera are very strain specific and generally allow us to see antigenic differences historically.

This is a summary of HI data from all of the collaborating centers performing this test. And you can see, by and large, when we use reference ferret antisera against an egg-propagated Michigan/45-like virus, which is representing the vaccine virus, you can see that the vast majority -- 96 percent -- of all the viruses tested are well inhibited by this antisera.

And only a low proportion of viruses show a reduction in titer of eightfold, or greater. And we consider that threshold as a low reactor or a variant antigenic variant. And I should say that this is also true, if we took antisera raised to the cell-propagated Michigan virus, we see a similar trend indicating that if we use ferret reference antisera, we don't see antigenic differences.

And this is an example of HI data. I know you can't see all these numbers, but again, just to orient you, along the top we have ferret antisera made to different reference viruses and down the columns on the left-hand side are 33 test viruses. So these are circulating viruses grown in cell culture and then tested in the HI. Highlighted in yellow are the responses of all the titers to antisera made against reference Michigan viruses. And so you'll see with high homologous titers, which is shown in red, that the test circulating viruses, by and large, are antigenically similar to the reference viruses, the Michigan/45 cell-propagated or egg-propagated viruses.

And this is a smaller test that was conducted at CDC. And again, highlighted in yellow there on the left are similar responses to ferret sera that we have raised to the reference Michigan/45 viruses grown in either eggs or cells. And you can see again, there's a number of test viruses. These are mostly -- well, all of them look like they're from the U.S. or Central America. And, again, these viruses are reacting at titers that are similar to the homologous titers that are in bold and underlined up in the top part of the panel.

The exception is these two viruses down the bottom from California and Pennsylvania. And these are showing reduced titers and we know that these viruses have an additional substitution at residue 156 and we know this is a key antigenic region and ferret antisera recognized this difference. But these other viruses that show no difference, they are all representative of this 6B.1A group that contains the S183P substitution.

So we couldn't see any difference using ferret antisera so, as in previous years, we had found

previously that sometimes we could see differences with human sera. So we took some individual pediatric sera from children that had been vaccinated with the current 2018/2019 season. We had a couple of age groups, and I'll show more of this data in a moment of our entire panels, but these were just some individual sera that we chose because they had good postvaccination titers.

You can see here, if we're looking now at the top, and then -- I don't know that this is going to show it either. Ah, yeah. Okay. So, if we look at the titers against the Michigan/45 reference viruses and then look down the columns, we can see that in many cases we're seeing at least a 4-fold if not an 8- or 16-fold reduction in responses to some of the newly circulating viruses in this genetic group, the 6B.1A with a 183P. And some of these reductions are as high as what we see with a known antigenically variant virus that contains the 156 substitution. These viruses are in the minority; very few of them are in circulation. But, as I mentioned, these are predominating.

Okay. So, to wrap up our analysis for the

(H1N1)pdm09s, as you know, we also perform what we call human serology. We receive panels of pre- and post-vaccination sera from different age groups, both from U.S. and the U.K. This table just represents the different populations that were used for analysis. And you can see here that we are now trying to expand the age range in terms of the pediatric population. So we have an older pediatric group, representing 9 to 16-year-olds as well.

So this is a representative test. It's a test that was conducted at CDC where we have -- again, what we're looking at is now we're comparing to the response. We've set the response to the reference virus, which in this case is a cell-propagated Michigan/45 representing the vaccine. We've set that response at 100 percent. And the actual numbers here represent the actual geometric mean titers of that panel, and each panel is about 20 or 25 sera.

So, what we're looking for is a substantial reduction. We set a reduction at 50 percent as being significant. So anything below that, we consider a

significant reduction compared to the response to the vaccine virus.

You can see that all of these particular circulating viruses that were in the test, they all contain the S183P substitution. And so, in some populations -- it's particularly noticeable in the pediatric and the older adult and elderly -- we can see a substantial reduction in antibody reactivity to these majority of circulating viruses.

And this is a similar picture we're seeing if we compare now to the reference virus that was grown in eggs, more similar to what was actually in the vaccine. We actually see a very similar picture where we're seeing substantial reductions, particularly in pediatric and in older adult populations. And even in some adult populations, it's right around our 50 percent threshold.

So, in summary for the (H1N1)pdm09s, these viruses predominated in many countries in Asia, Europe, and North America. And the vast majority of the viruses contain HA with genetic sequences that now

belong to a subclade 6B.1A. And they have an additional amino acid substitution at 183 with the substitution of a serine to a proline. And almost all recent (H1N1)pdm09 viruses, when we used ferret reference antisera, we could not see antigenic differences, and they were similar to the Michigan/45/2015 reference viruses. However, with some postvaccination pediatric sera, we did see reduced titers to these more recent viruses with the 183P compared with their titers to Michigan. And when we did our human serology panels at this reduction, it was also evident, particularly in pediatric and older adult populations.

So I'll turn now to our favorite topic, the H3N2s. So, H3N2 viruses were less widespread than (H1N1)pdm09 viruses this season. But there was quite a bit of local activity in the Northern Hemisphere, as you'll see by that salmon pink color.

And here, again, we have a phylogenetic tree of the H3 hemagglutinin. And what I'd like you to focus on here is, again, these. If we look across the

axis here, this is by month. So, I know you can't read this, but the last few columns here are the most recent months since September.

Shown here are the different genetic subgroups that we've talked about in previous seasons; particularly the 2a2s, you might recall were predominating last season. So, in our 2017/18 season, and it was still widespread in September for the vaccine decision that was made then. But you can see in the last few months, if you look at the bars here, there's far less 2a2 viruses and an increase in the density number of 2a1 viruses and also 3a viruses. And the 3a virus, as you can see, if you look regionally, the dark blue represents North America. So there's a lot of activity in North America. And hidden under there, there's also some activity in Europe.

Again, this is just to explain the quite extensive genetic diversity that we're seeing in the H3N2 viruses at this time. If we'll go from the top, this now -- and I'm sorry I can't really see this very well. If we go from the 2a1b viruses, they actually -

- there are three different subgroups that have different signature genetic changes, either a 135K which results in a loss of glycosylation. There's another group that has a 131K. And then there's a smaller group which seems to be fading out which has a substitution of N at 135, also with the loss of glycosylation at a neighboring site.

So, during this period, the data we had at the time of the vaccine consultation meeting was that the 135K viruses were predominating. But overall these viruses are really recognized as a group antigenically, as you'll see in a moment. Then, we have 2a2 viruses and as you can see that's a smaller group. However, down below we have the 3a viruses, and I just want to make a note that these -- you may remember the 3a viruses from when they first emerged back in '13/'14 when we had -- and 2014 onwards -- when we had that substantial antigenic drift that was comprised of both 2a and 3a viruses. And in the 2015/16 season, we actually had a 3a vaccine component, the Switzerland/2013. But since that time these 3a's have

really moved on and acquired a number of new signature changes; two of them at 144 and 193 that we know impact antigenicity. And so these current 3a viruses are not like the Switzerland of old 3a viruses.

And this is a pie chart just showing you the global distribution. Again, this was data at the time of our VCM. And we continue to monitor this, but you can see in North America that, at this point, about 50 percent of our H3N2 viruses were 3a; and a smaller proportion, about 20 percent, in Europe, again, given that Europe had regional H3N2 activity in different countries; and a small presence in Asia; but not really being -- as well as from South America -- but not really being seen much in Oceania or Africa at this point.

Looking at this, again, now with a timeframe, and what concerned us at the time of the meeting is, if you look at the green line, which is the 3a viruses, you could see since about November into December and January, there was a very steep increase in the proportion of 3a viruses and a decline in the 2a1b

viruses. And the 2a's shown here in the hot pink, I mean, they are just generally declining. So this is a very dynamic situation and is one of the reasons that we wanted to wait a little longer and see what happened here. But just the steepness of this climb of the 3a viruses was, to us, reminiscent of when the antigenically drifted viruses emerged in early 2014.

So, you'll also see there's is increasing diversity in the neuraminidase. This is a phylogenetic tree of the neuraminidase now. And the main thing I wanted to point out is that these 3a viruses now, also are reassortants. You might remember from my presentation last year, I talked about the 2a2 viruses that were predominating at that time, and how they had acquired the neuraminidase of a 2a1. So these were into subtype reassortants, and now the 3a's have done the same thing, suggesting that having this neuraminidase provides some advantage.

And what I didn't point out on the previous slide is you'll see where the existing vaccine viruses are; so Singapore and then this was the Switzerland

virus that was selected, which was a representative 2a2 virus that was selected in September for the Southern Hemisphere 2019 season.

So I'll turn now to antigenic characterization. And you might remember that this is increasingly more challenging for the H3N2 viruses because all of the viruses within the 3C.2a group are -- it's very difficult for these viruses to have -- in many cases these viruses don't have hemagglutination activity or a very low level of hemagglutination activity, which makes performing the hemagglutination inhibition antigenic characterization very challenging.

And in this particular example, this is a table, similar to what I showed with the (H1N1)pdm09s. It's a cumulative data from all of the collaborating centers. But you'll see only two collaborating centers represented here because the others, including CDC, could not have a stable cell-propagated Singapore virus that could stably have sufficient HA activity to test in the HI. And so more and more we're relying on and we believe the data more -- we lean more on the data of

virus neutralization, and I'll mention that in a moment.

But I wanted to show you this to show you that the HI data, in general, shows a similar trend to what I'll show you in the virus neutralization. And that trend is that if we compare with a cell-propagated Singapore virus -- the 2016 virus -- that the majority of H3N2 viruses are still antigenically similar to the Singapore. But note that these are two collaborating centers that did not see a lot of 3a activity.

However, if we now use antisera raised to an egg-propagated Singapore/2016 reference virus, we see that the majority of viruses do not react well with the sera, suggesting that antigenically they are different to egg-propagated Singapore virus.

And now turning to -- we're doing the same sort of antigenic characterization with reference ferret antisera, but we're using a virus neutralization assay. And all of the collaborating centers now use a focus or a plaque reduction assay.

So here again in this table, we're looking at

the response to antisera raised to cell-propagated Singapore/2016. And you can see the majority of viruses tested are well inhibited and a lower proportion are poorly inhibited. And at least the CDC data here, the vast majority of these viruses were the 3a antigen or genetically variant viruses; so indicating that they are also antigenic variants as well as genetic variants.

And this is the data, again, now looking at antisera raised to egg-propagated Singapore and we see the same trend that we saw in HI in that antisera raised to the egg-propagated Singapore, in general, does not cover well the circulating viruses.

And this is just a couple examples of the actual data. And this is a virus neutralization test performed at CDC. Shown in the yellow they are the responses, the titers to antisera raised to the reference viruses Singapore/2016 either grown in cells, or the X-307A which was actually a candidate vaccine virus, obviously grown in eggs.

We used this particular reference virus in our

hands at CDC because we knew it had genetically pure substitutions that were conferred by egg adaptation. Whereas, other reference viruses in our hands had a mixture, and we felt we weren't getting accurate estimates of the antigenic similarity or difference.

So, this really just demonstrates again that we have test viruses here that belong to either the 2a1b the group, the 2a2 or the 3a viruses. And the 2a2 and 2a1b viruses are generally well inhibited by antisera raised to the cell-propagated Singapore antisera, not so well against the egg. And the 3a viruses are poorly inhibited by either sera and stand out from the 2a1b and 2a2 viruses.

The same is true if we raise antisera to cell-propagated reference viruses belonging to the 2a1b group. They tend to cover the 2a1b and the 2a2 viruses, but not the 3a viruses. And the 2a2 virus -- antisera raised to 2a2 virus typically only covers its own genetic subgroup, the 2a2, and poorly inhibits other genetic subgroups. And then on the far right, we have the antisera to the Kansas/14/2017, which is the

reference virus for the 3a's. And you can see they well inhibit themselves in general and less well the other genetic subgroups.

And this is just shown using antigenic cartography from the University of Cambridge. And you can see quite clearly here how the HI data -- is this HI? No, this is neutralization data -- is clearly separating out the 2a2 group, which is represented by the Switzerland/8060 vaccine component from the Southern Hemisphere. The 2a1b viruses and Singapore sits within here. It's a 2a1 virus. And then in green are the 2a's which are clearly starting to form their own distinct subcluster.

So moving now to the human serology. I do just want to point out, again, most of the laboratories conducting serology for H3N2s are now, in addition to performing HIs, are also performing microneutralization tests. And you'll note that I'm not going to present the data, but I'll mention the result. We did have a panel, thanks to the FDA and DoD, we had a panel of adults that had been vaccinated with the cell-based

vaccine in the U.S. this season.

So this is set up the same way as I demonstrated for the H1 viruses. We're looking -- this is HI data. And again, we're looking only at egg-propagated viruses here because that's what we can test in HI. And compared with the response to egg-propagated Singapore, you can see that a couple of representative 2a1b viruses -- one 2a1b and one 2a2 virus -- are well inhibited by antibody that's been elicited from the Singapore vaccine. However, the 3a representative viruses is not well inhibited by antibody elicited by the Singapore vaccine. And you can see that is a constant pattern in the different age groups.

And this is now -- this is incorrectly labeled. This is actually a microneutralization test. The same layout here, we have, again, the different panels, representing different populations, but now we're comparing against -- so we're comparing against the Singapore reference virus grown in cells. And we have a number of different cell-propagated viruses of

the 2a1 and 2a1b group and a 2a2 virus. And, again, all of these are giving titers, geometric mean titers, that are comparable to what we see with the cell-propagated Singapore representing the vaccine virus. And the exception are the responses to the 3a viruses in most of the populations.

So, as I mentioned, we did do also some limited testing of a panel of adults that had received the cell-based vaccine in the U.S., and we saw very similar results. We saw, although the overall titers were lower, the homologous titers were lower, and in this case, we compared it to the North Carolina/04 which was the component of the cell-based vaccines. We saw similar titers with 2a1b and 2a viruses, but a drop in titer against the 3a's.

So, in summary, 2a1b viruses are predominant within the 2a clade. The 2a2 viruses have markedly decreased in this last period. However, 3C.3a viruses have reemerged, in particular, in December and January in diverse geographic regions. And the future relative prevalence of these two clades is uncertain.

Antisera raised against cell culture-propagated Singapore/2016 at the 2a virus recognizes the majority of 3C.2a and 2a1b viruses but does not recognize the new 3C.3a viruses. And alternatively, antisera against the 3C.3a viruses recognizes this genetic group, the 3a subgroup, quite well, but recognizes the 2a and 2a1b viruses less well.

Antisera raised against the egg-propagated Singapore/2016, representing the current vaccine component, recognize circulating viruses poorly. However, we found that if we looked at actual human panels that had received the Singapore vaccine, we found that the antibodies recognized most of the 2a1b viruses tested but not the 3a viruses. And antisera raised against the 2a1b group, even though they are predominating, they really recognize all test viruses poorly. This is -- sorry -- the egg-propagated 2a1b viruses that we have at this time.

Antisera raised against the egg-propagated 3a recognized, obviously, its 3a viruses quite well, but less well the 2a1b viruses; so a number of distinct

genetic groups and number of distinct antigenic profiles. And, at the time of the BCM, we did not have full characterization of potential candidate vaccine viruses, and that was the reason for the postponement of the decision.

So I'll move on to the B viruses. As we heard earlier, very little B influenza activity, both in the U.S. and throughout the Northern Hemisphere; this region only really sporadic activity. And if we look at all of the viruses that are reported based on sequence data, you can see that for those that where we have a lineage determination the -- so this the pie chart. This is just the B viruses reported to WHO where we had lineage determination. There was really equal Yamagata and Victoria lineage viruses shown in the green and blue respectively.

If we looked at the sequence data, you can see overall up until Week 52 of 2018, this was also true. But in recent weeks, it looks like there's a little more B/Victoria being reported and sequenced compared with the Yamagata.

This is just looking by region. You can see in some regions like Africa, there's more B/Victoria. Asia is about 50/50, and then varying degrees in other regions. But the B/Victoria is out there, albeit, the Bs overall at very low frequency.

So, moving to the B/Victoria-lineage viruses, this is again a phylogenetic tree of the hemagglutinin gene. Now we're talking about a much smaller number of viruses for the H1s and H3s. We had thousands of viruses characterized. Here we have a couple of hundred because the circulation has been low.

And, as you'll remember, in the last period last year or so, we've seen the emergence of this double deletion genetic variant that has a deletion of residues 162 and 163 in the hemagglutinin. We now refer to this as the 1A.1 subgenetic subgroup. And then we also had seen independent introductions of viruses that had three amino acid deletions, so 162 through 164. And these have been independently introduced and these viruses are still out there and we're seeing actually a slight increase in their

numbers in this current period.

Okay, just looking quickly at the neuraminidase, you can see that the -- again, these genetic groups cluster similarly in with the neuraminidase. We see the V1A.1 viruses generally clustering together, as do the triple deletion viruses.

And this is now understanding a little bit more of the circulation of these viruses. Again, this is just B/Victoria. Shown in red are triple deletion viruses. Shown in the yellow are the double deletion. And in the orange, the older V1A viruses that have no deletion. And you can see that these numbers are decreasing globally, as shown by the orange sectors in the pie chart and in the bar graphs.

And recently, although the numbers -- I should highlight some of these numbers are quite small. For example, the numbers in Europe, you know, we're talking single digits here. So, there does seem to be an upswing a little bit -- again, very low numbers of the triple deletion viruses; but overall the double deletion viruses are predominant in at least three

continents.

This is a little bit more about the distribution. So, in North America, the purple indicates the detection of both the double and triple deletions. Central South America is still only seeing the double deletions. And then in different parts of Africa, we are seeing triple deletions. And again, across Europe and Australia, we're seeing isolation of, again, in small numbers, both of these genetic variants.

So turning to the antigenic characterization, this is a hemagglutination inhibition test. Here I just want to focus you on this is the previous vaccine virus which represents the V1A group. This is the group that does not have amino acid deletions. The V1A.1, which is the double deletions, which is represented by the Colorado/2017 virus, this is the recommended vaccine component for the 2018/19 season. And then we have an antisera raised against a triple deletion. This is one of the earlier triple deletions from Asia. And we believe now what we're seeing is a

discrimination between the triple deletions that was seen earlier arising in Asia and ones that were detected first in Africa.

So, again, you'll see that antisera raised to the older virus represented by Brisbane, poorly inhibits all of these double and triple deletion viruses. The Colorado reference viruses cover the double deletion viruses quite well, but not the V1A without any deletion or the triple deletions.

And then we have a third group with the triple deletions where, in fact, this antisera is not covering anything terribly well. And we believe that these new triple deletions, they have an additional substitution at residue 136. And we believe that this may be having an effect, although we need further antigenic characterization of these viruses. But again, the numbers are quite low at this time.

This is just shown in an antigenic cartography where the yellow is the most recent period and the darker brown are the older double deletion viruses, forming a cluster here around the B/Colorado reference

viruses. Then, we have the older V1A here in blue. But with the current period, again, there are still some V1A viruses out there. And now these triple deletions are just popping up and showing antigenic distance from both the double deletion and non-deleted Brisbane-like viruses.

This is just a summary of that data that, again, as we've seen for influenza B viruses that do require egg adaptations. Once propagated in eggs, when we raised antisera to the egg-propagated viruses, they don't cover the circulating viruses as well. And we see some reduced overall reactivity there. But when we compare to the cell-propagated, we see that the vast majority of viruses are well inhibited by antisera raised to the cell-propagated virus, indicating that they are still antigenically similar to the current vaccine virus. And some of these viruses, no doubt, are either the older V1A or the triple deletion viruses.

Again, using similar panels of human sera, we did human serology studies. And this is slightly

different showing the combined results of all of the labs that performed human serology data. And we've just grouped the viruses into whether they had double deletions, triple deletions, or no deletion. And we're comparing the result so the geometric mean titers against the cell-propagated Colorado, which was in the vaccine, set at 100 percent.

And you can see that regardless of whether it was a double deletion virus tested, triple deletion -- and this is all viruses tested -- that we actually are seeing reasonably good antibody responses to these double and triple deletions from a vaccine containing the double deletions. So this is a little different from what the ferret sera told us, and so greater cross reactivity with human sera.

Turning finally to the Yamagata. Fortunately, this is our virus that is least exciting. It's good to have one of those. Again, all of the viruses in this period are still within the Y3 clade, and there's not a lot of genetic diversity that we see here.

Again, the neuraminidase, some genetic

diversity overall. In the last period, there was some acquisition of neuraminidase substitutions in the neuraminidase, but nothing terribly much to worry about we feel.

And this is just looking at HI data. This is some data from the Tokyo Collaborating Center, where, again, highlighted in yellow, you'll see the titers against the reference viruses either a cell-propagated Phuket/2013 or the egg-propagated Phuket. And you can see that compared with the homologous titers shown in red, we're getting fairly good reactivity with circulating viruses.

If we look at that by antigenic cartography from the University of Cambridge, we see the same clustering. The blue is the past seasons from 2016 to '17. And the yellow is the most recent period from January of last year to January of this year. And you can see very tight clustering still around the B/Phuket reference viruses, suggesting that there's no antigenic change here.

This is just summarized again. Again, we see

that somewhat reduced coverage when we use antisera raised against egg-propagated Phuket, 64 percent overall. And there is some variability here. This is, for example, the Australian lab. This is difference in ferret antisera that are used in some labs; but by and large, there's still very good coverage shown in the other labs against the egg-propagated Phuket reference virus.

Similarly, as to what we saw with the B/Victoria, this is, again, now we're looking at a compilation of data from multiple labs. We're comparing the HI geometric mean titer against the Phuket/3073. I believe, yeah, this is cell-propagated. So again, we're not seeing any real hint of substantial reductions in titers when we look at the antibody elicited by the current vaccine and its ability to react with circulating viruses.

So, in summary, B/Yamagata and B/Victoria lineage viruses did co-circulate, but at extremely low levels in this past period. And they were isolated roughly in equal numbers overall. But, by region,

their proportions did vary.

For the B/Victoria lineage all the viruses still belonged to clade 1A. However, we're seeing a steady proportion of viruses from many countries now are these double deletion viruses that have the deletions at 162 and 163 in the hemagglutinin. And in this period, we have seen an increasing number of viruses that are also encoding a triple deletion.

Most of the viruses with a deletion of two amino acids in the HA react well with ferret antisera to the reference B/Colorado virus. But viruses that don't have the deletion or have the triple deletion and not reacting well with that antisera, indicating that they're antigenically distinct. However, when we look at the human serology, we saw that HI antibody titers against the Victoria lineage viruses, whether they had two, three, or no amino acid deletions were comparable to what we saw with the reference B/Colorado self-propagated virus.

And for the Yamagata lineage virus, these all belong to clade 3. Recently circulating viruses were

well inhibited by cell- or egg-propagated reference antisera against cell- or egg-propagated Phuket/2013. The human serology studies only showed some modest reductions in post-vaccination HI GM titers against representative circulating viruses when compared with the reference Phuket viruses.

So, as we've heard, our recommendations were to move to A/Brisbane/02/2018, and that's a reference virus that has the characteristic 183P substitution. As we know, the H3N2 decision has been deferred until March 21. And there were no changes made to the B/Victoria or B/Yamagata lineage. And for the trivalent, again, it was recommended that the B component be the B/Colorado/2017. So that was similar to last season.

So I just want to thank all of my colleagues and say this is the last time I'll be here in person. I'm retiring in a couple of months. I'm seeing some people look at me. But I wanted to introduce Dave Wentworth, who's here in the audience. He is currently the chief of the Virology, Surveillance, and Diagnosis

branch at CDC. His team generates all of this data for CDC. And he will be taking over at the collaborating center, and so the person that you will be seeing here one year from now. So I will be on the call on the 22nd, but after that, I wish you well. Thank you. So, any questions?

DR. EL SAHLY: Dr. Edwards.

DR. EDWARDS: First of all, Dave has big shoes to fill. We thank you for so much wonderful information you've given us for so many years.

I have a couple questions about understanding the delay in -- is the reason that it's been delayed because you need to sequence more viruses? Or is it because it seems to be a bit changing in terms of going up and going down? So could you just -- or is it both?

DR. KATZ: It's both, but I mean as we heard earlier, one of -- a key requirement for us to make a recommendation is that we have a new candidate vaccine virus that is characterized, that can be rapidly handed to manufacturers. And so, one reason for the delay is that we're still in the process of fully characterizing

the viruses. And we while we had reference viruses, we did not have the high growth reassortants, either in our hands or fully characterized, depending on the genetic subgroup. And so we felt we needed a bit more time for that.

And also, we felt that this time would allow us to continue to monitor the dynamics of these two genetic groups and particularly try and understand, certainly in recent weeks, the 3a's are really taking over among the H3N2s in the U.S. We're still trying to understand if this trend is also being seen in Europe and Asia and elsewhere. We know the 3a's are out there in higher numbers than they have been in recent seasons, but it will allow us a bit more time to see those trends.

DR. EL SAHLY: Dr. Bennink.

DR. BENNINK: Yeah. First, I want to thank you as well, Jackie, for everything over the years and everything else. But also this year for the human sera data and particularly the pediatric, which really, I think, is pretty informative from that standpoint, so

that is really nice actually to see.

One question on the H1 is, in the table that you had in here with the H1 analysis of a recent circulating pandemic 109, where does the suggestion that you have, the Brisbane, which one is it most like in that list of viruses? So, what it sequences, which one is it closest to?

DR. KATZ: Are you talking about these?

DR. BENNINK: No, not this one. It's like this.

DR. KATZ: Right. Right.

DR. BENNINK: Yeah, that. Where would it be?

DR. KATZ: So, maybe I can answer that better by --

DR. BENNINK: I didn't see a cartology either --

DR. KATZ: I glossed over. I forgot to mention, it's right there. But Brisbane is more at the base of these, and you can't see exactly where it is. But it's somewhat more at the base of this emergence of the 183P, so it doesn't have additional substitutions

that are forming new sort of clusters, emerging clusters. So, again we felt it does represent the 183P group, but it's more at the base of the tree and sometimes we feel that it provides better -- it's more likely to be reactive with more of the genetic subgroups that have additional mutations.

DR. BENNINK: Off the top of your head, though, if you go to that other table.

DR. KATZ: Yeah, I'm not sure.

DR. BENNINK: The spreadsheet. And you may not be able to and if you can't, you can't. Keep going back.

DR. KATZ: Hang on.

DR. BENNINK: Keep going. There.

DR. KATZ: Yeah. These are all --

DR. BENNINK: Is it anywhere so that we could make a comparison with what the titers are? That it's closer to one of those viruses?

DR. KATZ: Yeah, unfortunately, that was the other thing at the time of this announcement was that the Brisbane/02 had been mostly characterized by the

Australian lab that isolated it. So it's not on any of these, but it should be -- I believe it should be up in here. It should look like this.

DR. BENNINK: Okay.

DR. KATZ: Yeah.

DR. BENNINK: Another question which is kind of, I'll say, a little bit of a crazy question, but has the WHO or you ever considered as the quadrivalent, the fourth virus in this case, instead of another B putting up a second H3 in?

DR. KATZ: Yeah, I get that question a fair bit. I think we haven't really considered it because I think FDA probably needs to address that. I don't know whether that would require a different licensure requirement of vaccines or not. But I must say, even our fitness forecasting modelers that are now contributing data, they said that this diversity, for H3N2s, in particular, is quite extraordinary. We haven't really seen it before, to this extent.

DR. EL SAHLY: Dr. Weir.

DR. WEIR: Yeah, I think all of the scenarios

you're thinking about adding yet another component or substituting one would have to require clinical data and would change the license. Just like when we did the addition of a fourth strain, the second B strain, every manufacturer had to amend their license and get clinical data to support that.

DR. EL SAHLY: Dr. Monto.

DR. MONTO: Just a comment and a question about the H1N1. We went six or seven years without a change in the H1N1, and here it's, after a couple of years, we're changing. I was surprised about the response of the pediatric group to the proposed strain, because it looks like there's some imprinting going on. Is there any way to try to figure this out, in terms of the previous change?

DR. KATZ: Yeah, probably not with the data we have right now, but we could look into that. I mean the one thing -- I mean, serologically it's quite clear. We're seeing reduced responses. The VE was not that bad in young children. It was in at least with the U.S. VE and with, I think, some other European

countries, perhaps Spain, in some of the preliminary interim data, the adults were the one, again, that looked like where the VE was declining.

DR. EL SAHLY: A question regarding the antigenic relatedness using human data, human sera in the B/Victorian and B/Yamagata. Initially, you set it at 100 percent, but then there were a couple of age ranges where there's a big drop off. And I was wondering if it has to do with the numbers tested or it has to do with a particular age range issue?

DR. KATZ: Okay, let me just -- okay, I think I'm exhausting the mouse here. So it was for the B/Victoria?

DR. EL SAHLY: Yes. Here.

DR. KATZ: Right here.

DR. EL SAHLY: Yeah.

DR. KATZ: Okay.

DR. EL SAHLY: So this lower sera activity in, I'm guessing, the 6 to 36 months and the 3-year-old are because of low numbers tested or is there a difference in responses that is true there?

DR. KATZ: It's probably reduced responses compared to some of the adult populations. So, you're looking at -- I'm trying to figure out which ones you're looking at.

DR. EL SAHLY: Double deletion egg.

DR. KATZ: Oh, they may not have been tested.

DR. EL SAHLY: Okay, so it's an issue of numbers.

DR. KATZ: If it's that low, they haven't been tested. Sorry.

DR. EL SAHLY: Ah, okay.

DR. KATZ: It's a factor of volume.

DR. EL SAHLY: Volume, numbers. Okay. All right. Thank you. Additional questions to Dr. Katz? Dr. Monto.

DR. MONTO: I may have missed it, but where does the sequence data come that's used for the flu block for vaccine?

DR. KATZ: So they look in GISAID. They look at the WHO recommendation. And then they will use a sequence that's either from an original clinical

material or from a very early cell-propagated passage, and those two sequences should be essentially the same. That's my understanding what they use.

DR. MONTO: What role does FDA have in this, in their selection? Well, usually there's a choice given of which viruses to use to propagate for either the cell-culture based or the egg-based. And this comes in the recommendations. How does that work?

DR. WEIR: So they're slightly different situations. For the cell-based vaccines, there will actually be a cell-derived -- CBV or reference virus. And that will go through the normal channels with the WHO Collaborating Centers and go through the two-way testing and get approval and listed on the WHO website. And so only those viruses can be used -- well, are acceptable for use -- by these cell-based manufacturers.

For the recombinant vaccine, it's a little different because, of course, it's changed over the years. Originally, the sequence was typically probably the egg-based virus because that's what everything was.

But in the last few years, they have gone back to using the original sequence of the wild type that's been in the database. And we do look at those sequences.

DR. MONTO: You do look at them.

DR. WEIR: Yes. I mean, because you can imagine they actually have the ability to change those sequences at will. So, yes, we do look at them and it's usually the wild type sequence.

DR. EL SAHLY: Okay, we have with us on the webcast, Dr. Beckham. Dr. Beckham, would you please introduce yourself, your affiliation, and your expertise?

DR. BECKHAM: Sure. Thank you. My name is Tammy Beckham and I am a veterinarian by training and have a background and infectious diseases. I am the acting director of the National Vaccine Program Office. So thank you very much.

DR. EL SAHLY: Okay, Thank you, Dr. Beckham. Well, Dr. Katz, the ability to distill so much information and make it accessible is remarkable. Thank you for all the years.

Next with us from the Department of Defense is Dr. Mark Scheckelhoff. I hope I said your name right. He will review the Department of Defense Vaccine Effectiveness Report.

DoD VACCINE EFFECTIVENESS REPORT

DR. SCHECKELHOFF: All right. Good morning, everyone, and thank you for the opportunity to present the DoD influenza surveillance and vaccine effectiveness data. As she mentioned, my name is Commander Mark Scheckelhoff. I'm with the Defense Health Agency, part of the Armed Forces Health Surveillance Branch, and the Global Emerging Infectious Surveillance Program, the GEIS program.

The data I'll be presenting today is generated primarily through our partners: United States Air Force School of Aerospace Medicine, USAFSAM, which is in Dayton, Ohio; the Naval Health Research Center, which is in San Diego, California; as well as the Epi and Analysis Group at the AFHSV here in Silver Spring.

So just a disclaimer that the DoD is not on the hook for anything that I say today.

Just a quick outline of what I'm going to be covering. I'll give a quick overview of the program itself, the DoD Influenza Surveillance Program; go through the strain circulation that we see in the current season, up to this point across our network; the phylogenetic analysis -- again, that was performed by the folks at USAFSAM; and some preliminary vaccine effectiveness estimations.

So, the DoD surveillance program, again, covers about 400 locations over 30 countries, certainly not the numbers that you see with the WHO data. These are primarily military members, but we also have a number of relationships with ministries of health, ministries of defense. So it does include some foreign national data as well, as well as some academic collaborators.

All of our core laboratories have extensive characterization capabilities, so we do have the ability to do our RT-PCR, culture, as well as sequencing, and some serology. We do share the results throughout the year with CDC, WHO, as well as obviously

our geographic combatant commands within the DoD.

We also in house, here in Silver Spring, have the epi and analysis capability so, you know, over a million active duty records, access to all those data that can be used basically to produce the monthly reports. We get ad hoc requests for a variety of different analyses for different studies and analysis. And then obviously during the influenza season, we're generating weekly reports and the data that we'll be sharing here today.

This is just a quick snapshot of the surveillance footprint for DoD. All of the stars on the map represent where we have a core laboratory capability. The more darkly shaded countries are active participants in the Influenza Surveillance Program. Obviously with the DoD, the consideration and part of the strategy behind selecting or, you know, perhaps constraining the countries that are involved are those that are of interest to DoD -- where troops are, where troops may be going. So we don't have the ability to necessarily cover all the different regions,

but we certainly have a fairly wide footprint.

Starting off with the subtype circulation for, first, North America. So this is primarily military members, including recruits. It also includes some military dependents, as well as some civilians. We've been doing some increased surveillance down at the southwest border with the current activities there. So these numbers include some of that data as well.

Very similar to the other data that you've seen, on the graph to the left, the left axis is the number of specimens by week on the bottom access and then the percent positives on the right-hand side. The different colors are indicative of the different subtypes of influenza. We're showing back from the 2016/2017 season all the way through approximately about Week 4/Week 5.

Again, similar to the numbers that have been presented already, H1N1 has predominated throughout the season. Not shown on this chart, but again similar to some of the discussions that have already occurred, we have also observed some regional pockets of H3N2

throughout the season. But in the more recent weeks, particularly Week 8, we've seen that the H3N2 has basically flipped the predominance. While we were having like a 75/25 split to H1 to H3 in some of the earlier weeks, that ratio was basically flipped. And in Week 8, I think it was pretty close to 70/30; 70 percent H3N2 and about 30 percent H1N1. Again, similar to some of the other data, very low prevalence of any influenza B in North America thus far in this season.

For South America, primarily, these are, again, U.S. military and civilians. We also have some local military and local civilian populations represented in this data primarily from Peru, Honduras, Paraguay, Bolivia, and Colombia. Again, a lot of those are primarily in the tropics, so you see a little bit of a different curve in terms of prevalence. We have basically seen primarily, again, H1N1 in these regions, but we've also seen some emerging H3N2 in this region as well.

In terms of the data from Europe, these are primarily military members and their families that are

stationed in either Germany, Italy, Spain, Turkey, Great Britain, or Kosovo. Throughout this season we've actually had fairly low incidents of influenza, up to this point. Again, this is data leading up to about Week 4/Week 5. And similarly, to the data in North America, in the most recent weeks, there's been a certain uptick in the incidents of H3N2. Earlier in the season, it was a fairly even split between the two subtypes. And in the more recent weeks, there's actually been an uptick in incidents in general, and associated with that increased incidents was an increased proportion of the H3N2 subtype.

For the Middle East, obviously, the DoD has a strong interest in what's happening in the Middle Eastern countries, primarily the U.S. military service members, and as well as some of the select local populations in Afghanistan, Iraq, Jordan, Kuwait, and Qatar. We've got very low numbers reported from that region. It has been H3N2 has been the dominant subtype that we've been observing so far this season. There has been some H1N1 kind of at low levels. And, again,

similar to the other locations, very low levels of influenza B so far this season.

We actually split out our data from Africa into two regions. The East Africa region consists primarily of Kenya, Tanzania, and Uganda. And these are representing actually primarily foreign military and civilian populations. There are some gaps in the reporting. One of our core laboratories in Kenya had some supply issues getting reagents that we're trying to work out. So, some of the numbers are reduced not because of reduced incidents, particularly, but because of some testing issues that were occurring there.

Regardless, the H1N1 dominated very early in the season. H3N2 has been the predominant subtype in more recent weeks and for more of the season, actually. And we actually have seen more than any other regions anyway but still a low number of influenza B circulating in that region.

These are countries in kind of the eastern transmission zone. We split out West Africa; it's primarily Ghana, but it is certainly a different

transmission zone for influenza. Again, this is foreign military and civilian populations within Ghana. Again, you see that there was some predominance of H1N1 early in the season. However, there was kind of this fairly strong proportion of H3N2 and, again, much higher than in other regions influenza B surveillance incidents occurring in this area. The incidents have dropped off a little bit in more recent weeks. And the incidence in proportion of H1 and H3 has kind of evened out to be more even as well.

The data from Asia, so this is primarily Eastern and Southeastern Asia transmission zones. So we're talking about both U.S. military populations as well as some local national populations, primarily in Cambodia, Thailand, Republic of Korea, but also the Bhutan, Indonesia, Japan, Nepal, the Philippines, and Guam as well.

So there was a dominance of H3N2 early in the season. More recently, H1N1 has predominated throughout the more recent weeks. There is still a fair proportion of H3N2 circulating in our populations

there. And, again, you can see that there's a smaller proportion, but influenza B is present and being detected.

Just a summary of the circulation activity to date. In North America, again, very similar to the data that you've seen thus far. The predominance of H1N1 was kind of the story up until very recently. And in those just most recent weeks, we've seen a dramatic shift in the predominance and frequency of H3N2.

From South America, again, H1N1 was predominant, recent elevation of H3N2. But again, those numbers are a little bit more reduced because it's their offseason.

Activity in Europe has been fairly reduced compared to what we've seen in North America. But again, I could add that little caveat to this as well, that in the most recent weeks we've seen a little uptick in the activity. And that activity has kind of shifted what was previously a fairly even mix to be much more predominant H3N2.

Then Asia data, the data we got from Asia,

again showing an early, very early predominance of H3N2, but with a more recent predominance of H1N1 to now actually kind of a more even split between the two. Whereas Africa, we've seen more of a predominance of H1N1 very early and then more of a shift to H3N2. And then the Middle East, H3N2, despite the low numbers, has been kind of the more predominant virus throughout the season.

Now going into the phylogenetic analysis of the strains that we're observing in circulation throughout the DoD. We focused in, obviously, on the Northern Hemisphere strains, since that's what we're informing here today. This is a pie chart just showing the viruses and their source. So primarily, these are coming from North America, a fair number from the East and Southeast Asia surveillance, as well as smaller proportions from the Middle East and Europe.

Starting off with the influenza A(H1N1) hemagglutinin from this current season. So this is laid out very similarly to Dr. Katz' in terms of if you look the -- does this have a pointer? Yes. So down

here is by month. The different colors over here are representative of the source of that strain. The current vaccine, the A/Michigan -- let's see down here at the bottom and the proposed A/Brisbane is circled and in red font up above.

So, again, very similarly to what's already been discussed, this 6B.1 clade and this very kind of rapid predominance and almost exclusive circulation of the subclade 6B.1a is also displayed in our data. We also are observing this S183P. I don't have them specifically marked off, but you can see them again popping up throughout the diversity of the 6B.1a subclade. So we're certainly observing that, as well as the T120A mutation as well.

As discussed, most of this data is coming from North America, which is why you see so much blue. There's this little pocket here of viruses with some additional diversity from -- or kind of a cluster of its own diversity here from Southeast Asia. But we're also observing the subclade generating and demonstrating a lot of genetic diversity, which is very

similar to the data, again, that you've already seen.

From the neuraminidase perspective, again, it looks very similar to the hemagglutinin data. We do have, again, this little cluster of viruses from Southeast Asia that are very similar. Again, primarily most of this is coming from North America. Again, the clade looks very similar to, and the diversity looks very similar to, what's being observed in the hemagglutinin.

One just quick note, there's five viruses that had the S247N mutation right here. I believe they all came from North America. But that is one of the mutations, obviously, I think you're all aware that has shown to confer some resistance to Tamiflu. So just something interesting to keep an eye on.

Switching over to influenza H3N2, this is the much more interesting and concerning diversity that we're seeing. So, again, very similarly, you know, we had observed the prevalence of 3C.2a2 in last season, as well as 2a1b subgroup. And in this season, you know, we're seeing, again, in more recent weeks and

primarily in North America, this emergence of the 3C.3a clade. Again, so the current vaccine strain is here in red. And this A/Switzerland strain that circled in yellow was the suggested or the Southern Hemisphere vaccine component.

So just looking at this in a different way, to kind of reemphasize the prevalence of the 3C.3a, this is the incidence of H3N2 over the past two seasons. Again, last year you see that huge numbers of 3C.2a2 in circulation, still fair numbers of the 3C.2a1b, and very low levels of the 3C.3a.

Then, when you kind of zoom in on what's occurring in this season, we're still getting a fair amount of the 3C.2a1b. So it seems like that's a pretty fit virus that's going to be able to hang in there for a while. But very reduced levels of 3C.2a2, especially compared to last year. And then again this recent emergence and predominance of the 3C.3a. Again, this is primarily all from North America that these viruses are being generated.

I'll just note that the February data lack of

numbers there is not due to lack of incidents; we just haven't had a chance to actually get that sequence and populate the slide. So that's not due to any sort of drop in prevalence.

Moving on to the influenza A(H3N2) neuraminidase sequences that we've been observing this year. Again, the clade structure basically mimics what was observed for the HA. And, again, we see this primarily North American group that's been emerging.

Now, moving on to influenza B. So this is B/Victoria, the hemagglutinin analysis. Again, for both the B/Victoria and B/Yamagata, we have relatively low numbers of sequences, just due to the low prevalence, so far this season. There's only 26 B/Victorious sequences.

But, again, very similar to what's already been discussed, we're looking primarily at the V1A-2Del clade, which is this group here. Those are primarily, again, from North America. We have seen some of the emergence of the three deletion viruses. I'll caveat that by saying, if you look here on the

chart, we had a group of around ten viruses that came in all from Thailand that were basically genetically identical.

So, with the low numbers and seeing that little cluster, it's kind of hard to break out how important that is at this point, if that was just, you know, one family that all got sick and just circulated the same exact virus, or if that is actually a more widely distributed virus in the region. But again, those are primarily being observed in Southeast Asia; although we do have a couple incidents of it occurring in North America as well.

Again, just kind of looking at it in a different way. So last season, this two deletion V1A.1 predominance with basically no three deletion circulation. And then into this season, again, low numbers, so a little bit difficult to make any real interpretations of this data yet; but you do see certainly a circulation, a much higher incidence of the three deletion viruses, so far.

Then moving on to the B/Yamagata, as well as

Dr. Katz already mentioned, this is pretty boring. Everything is all in clade Y3. Again, we have relatively low numbers. This is, again, the virus, the vaccine candidates strain there. Everything seems to be -- there seems to be fairly low genetic diversity in the group. Everything, again, is still kind of maintaining in the same clade.

Then just to summarize what we're seeing in terms of protein homology compared -- the current sequences compared to the strains that are listed. Notice that all of them have fairly high homology. I'll just note that this initial analysis was done on the current vaccine strain.

We also ran the numbers versus the A/Brisbane proposed vaccine strain. Not surprisingly, based on its location within the subclade, these numbers did go up a little bit, about a half a percent. But again, these are all fairly, fairly high to begin with. Homology doesn't necessarily directly reflect antigenic composition or comparability, but just a good snapshot. And for the Bs, again, very high homology.

I'll just say that the neuraminidase sequences was not available for all of the B/Victoria, especially some of those three-deletions strains, which is why this protein homology over here is so high. That's probably a bit of a sampling artifact. So, as we get more data in, I'm sure that will not quite be so high.

Vaccine strain recommendations, again, just based on the genetic data that we've been observing throughout the DoD surveillance network thus far. The A/Brisbane strain is certainly well represented in the diversity of the clades and the sequences that we've been observing. We are also seeing these kinds of generations of smaller clusters that seem to be forming and increased diversity within the subclade that's currently circulating; but we're not seeing any of those gaining any predominance over another. Again, very similar to what Dr. Katz presented.

For the H3N2, obviously, this emergence of the 3C.3a clade is interesting and needs to be taken into consideration. So, again, that's postponed until later this month. For the B/Victoria component, the

B/Colorado, again, is very well represented in the sequences that we've been generating. And for the quadrivalent, again, the B/Phuket, there's been very little change or diversity and Yamagata strains. So that appears to be a good choice as well.

Moving on to the mid-season vaccine effectiveness estimates that are being generated by the DoD. Again, these are these are created by three separate groups, representative of three separate populations. So, one was generated by the Air Force Satellite School of Aerospace Medicine, USAFSAM. Again, one was generated by Naval Health Research Center, NRHC, in San Diego. And the other was pulled from the Epi and Analysis Section here at AFHSB, Armed Forces Health Surveillance Branch. I'll go through each one of the different populations that those represent as I go through the slides.

All of the studies were case test-negative control methods. They are very similar to what was again presented earlier. And for the data generated by USAFSAM and NHRC, these are lab confirmed by either RT-

PCR and/or viral culture. One just quick note, AFHSB pulled and included positive rapid test, but excluded rapid test-negatives. And again, the analysis was performed for all of the influenza types and subtypes.

Starting with the analysis from USAFSAM, so this population is the DoD healthcare beneficiaries. This excludes the active duty component. The data includes that from early December to mid-February; and analysis, again, by each of the influenza type and subtype; as well as by populations overall, in children and adults. We adjusted for age groups; the data collection; the region, either Eastern CONUS Western CONUS or OCONUS; as well as gender. Just a note, we did run the numbers for influenza B, but they were so low it really was -- so it's not included here because the numbers are so low.

Laboratories contributing specimens for this analysis include USAFSAM, about 1500; Landstuhl Regional Medical Center in Germany; and Brooke Army Medical Center in San Antonio. We had 645 cases, again, confirmed by either RT-PCR or culture and, the

controls just under 1500. Again, these are test-negative controls. The vaccination rates are shown there. Cases are about 48 percent, controls were at 64 percent. Of the total cases, you can see the breakdown here, fairly evenly split between H1N1 and H3N2. And, again, the numbers for influenza B were so low that they're not going to be included in the additional analysis that I'll be showing.

This is just a breakdown of the age groups. The cases do tend to be a little bit younger than the controls. And so this is the crude and adjusted vaccine efficacy rates. This is a little bit hard to read, so it's actually a little bit easier to show this using the forest plot on this chart.

You'll see overall, the VE adjusted vaccine efficacy rates are in the upper 40s, when you look at it overall. When you look at A broken out as, again, the entire population versus children or adults, again the rates are again, very similar to that which has already been presented and discussed, in the kind of upper 40s, around 50 percent.

Interestingly, when you start breaking it out by subtypes of either H1 or H3N2, you see this; our highest VE estimates are for children with the H1N1 at 66 percent. The adults were significant, but they had a much broader confidence interval. So not quite as strong there. And when you look at the H3N2, the one number that actually wasn't significant was this group of children. Again, the point estimate is suggestive of production, but it was not significant. Whereas, the adult population that was observed in this group, also had a very high VE of 67 percent, which was pretty dramatic.

Overall, the vaccine seems to be moderately protective, was significant for, again, all groups except for that H3N2 adjusted for among children. And the highest rates we saw were H1N1 among children and the H3N2 highest among the adult population.

The NHRC, so Naval Health Research Center analysis, this is specifically looking at the southwest border population, as well as active duty military recruits. It also includes some beneficiaries that

received care at DoD military, with the assumption that those did not go into the clinical records that were just presented. I'll just caveat that by saying that there might have been one or two cases where there's potentially a double count with the previous data.

Again, crude and age-adjusted VE will be presented. We had 251 cases. These were all confirmed by real time PCR on a little over 1,100 controls. And the vaccination rates, again, are demonstrated there. Cases was about 13 percent and control is a little over 25 percent. This -- I apologize. This is actually a typo of the prevalence -- was 91 percent H1, and H3 was only 8.4 percent. And as you see, we didn't have any influenza B in this population.

The age distribution. It's broken out like this because this is how the data was categorized from the border clinics where we got much of our data. So, we didn't want to try to restratify the recruit populations. So we just categorized them all in this way. And, again, the cases do still tend to be a little bit younger than the controls for this group.

The data for the VE estimates for this population: because the number of H3N2 were so low, we adjusted influenza A overall, and then broke out H1N1 separately. These estimations, again, whether you look at overall, zero to 17 years, 18 to 64 years, or over 65 years, we had significant protection in all groups except for the 65 and over age group. This is, I'm guessing, primarily because the sample numbers for this group are so low, again, you see the point estimate is relatively good, but the confidence interval is very wide, so we're not able to make any statistical significance statements regarding those.

Overall influenza A, fairly good vaccine effectiveness estimates. And, again, when you break out the H1N1, it actually gets even stronger for overall, as well as the 0/17 and 18 to 64-year age groups. So again, protective and significant for all groups except for that 65 and older group; highest for the 18 to 64, when you look at the H1N1 specifically, and that was around, almost 70 percent. So very, very high. And, again, the H3N2, there was only 21

infections identified. But when you look at the overall estimates, the vaccine effectiveness was still fairly strong in this population.

Now moving on to the AFHSB, this is the Epi and Analysis Group. So, this data is coming directly from the active duty service members; so Army, Navy, Air Force, Marines, both CONUS and CONUS -- CONUS and OCONUS, sorry. Again, looking at basically from early December to mid-February. Again, these included rapid positive tests, but also RT-PCR culture. Again, test-negative control method was used, and the models were adjusted for gender, age group, date of diagnosis, and we also included a five-year vaccination status. And it will play out in the data, but again, DoD, we're a highly vaccinated population, so it makes these VEs a little bit challenging.

So that just played out or are kind of demonstrated here on this chart. So cases had a 91.9 percent vaccination rate, controls at a 91.1 vaccination rate. Just a note, this season, DoD basically purchased the inactivated egg-based vaccine.

That was the primary type distributed amongst the DoD active duty service members, so that is the only type of vaccine that's included in this analysis. And 92 percent of the subjects had prior flu vaccines in the previous five years. So again, we're just dealing with a very highly vaccinated population.

Influenza A not subtyped. We had a little over 1,200 cases. And then, again, a pretty even split between H3N2, H1N1. And for this analysis, we were able to pull a fair number of influenza B as well.

So case/control breakdown for this population. In this case, actually the controls are a little bit younger than the cases. Again, we don't have anybody less than 18 years old because we're only talking about active duty military. And we don't have really many people in the 40 and above age group as well.

When you look at the vaccine effectiveness estimates, none of the data are significant. Again, primarily because we're dealing with such a highly vaccinated population. We do see point estimates that would be suggestive of protection. But, again, nothing

that's statistically significant. And, again, just -- no significant VE estimates. They were slightly better for A(H1N1) than H3N2.

Then this is just, again, a summary of the overall results. Again, looking at the data from USAFSAM, which included the dependents, we had -- as well as the data from an NHRC, we had statistically significant VE basically overall. I think the range was in the upper 40s near 50 with some subpopulations. Looking at the specific H1N1, again, had a fairly strong VE of around 65 percent. But again, all the active duty populations were not statistically significant.

Okay, so overall, again, the estimate was around 47 percent, ranging up to close to 60 percent, so indicating some minor protection and, again, best for the H1N1.

Just some quick statements on the limitations and how generalizable is this data. The subjects were medically attended, so we did not assess vaccine impact on less severe cases. Again, I already mentioned the

caveat about the military population and how this kind of negatively impacts the ability to estimate VE.

There's been a number of studies about the impact of repeated vaccination and if that somehow starts to attenuate the immune response with these repeated exposures. That's certainly something we're interested in and there's a number of studies going on to try to evaluate that. I don't have any data that can kind of speak to any of those specific issues at this time, but we're in the process of collecting that, as well as doing the comparisons between the egg-based and the cell-based vaccines.

Again, this season, the DoD primarily distributed the inactivated egg-based quadrivalent vaccine; so there's no ability, at least internal to DoD, to do that comparison. But we'd certainly be interested in comparing our data to other populations that received different vaccines and see if there's some way to start to tease that out as well.

So I just want to thank you, again, for the opportunity to present the data here. I just want to

quickly go through -- I have a very long list of contributors and partners. 65th is in the Republic of Korea; the AFRIMS group in Thailand; Landstuhl and Public Health Command in Germany; NAMRU-2 in Cambodia; NAMRU-3 is kind of split between Ghana, Sigonella, Italy, Jordan, and Cairo; the NAMRU-6 group, which is South America, Peru, and Honduras; again the NHRC crew out in San Diego; and there are folks with CDC-BIDSs; and the California Department of Health; USAMRD in Kenya and their affiliated group out in Tanzania; the core group here at a AFHSB in Silver Spring; a special thanks to Dr. Cost who is with the Epi and Analysis Section and she helped do the vaccine advocacy; as well as Ms. LeeAnne Lynch, who helped pull all these slides together. We are the team of two that do the respiratory surveillance for the GEIS program. So, I certainly couldn't have done this without her help. And then the AFHSB Air Force satellite; and the folks at USAFSAM that did both the VE estimates, but also put together the phylogenetic analysis that I presented here today. Thank you.

DR. EL SAHLY: Thank you, Dr. Scheckelhoff. I guess I'll begin by asking when the vaccination coverage rate is 90 percent -- 92 percent or so, what can a test-negative design tell us? I mean, should we be examining this data in a different way to get, I guess, a different angle of the story? Because the test-negative design when everyone is at 92 plus percent vaccinated is probably, as you demonstrated, a bit less informative.

DR. SCHECKELHOFF: I'm certainly open to suggestions.

DR. EL SAHLY: That's for the epidemiologists and statisticians amongst us. Yes, Dr. --

DR. WIESEN: I just have a separate question.

DR. EL SAHLY: Oh, separate.

DR. WIESEN: This is Andy Wiesen from DoD. Yeah, there is some concern with that design, given the fact that it says the vaccine doesn't work in active duty; and that would lead us to say, well, why are we doing in the first place? So my guess is that those people who don't get vaccinated are different, somehow

that was not -- it's not apparent from the study design. Because everybody's required to get the vaccine unless they have a medical or some rare administrative exemption. So, either you are avoiding it and you never got tracked down, or there's something else.

So that is problematic in that study design. So, yeah, I would say that that needs to be really looked at more carefully if we're going to use active duty service members and generate an estimate. It needs to have some kind of a validated design because we shouldn't be getting disparate answers.

DR. EL SAHLY: Dr. Offit and then Dr. Meissner.

DR. OFFIT: Yes, as just a corollary to this issue. Why wasn't the immunization rate 100 percent? These are active duty military, right? I mean, so am I assuming -- I mean, why wouldn't they get a vaccine? It can't -- and if it's a medical contraindication, what would that medical contraindication be? Egg allergy's not a contraindication anymore.

DR. SCHECKELHOFF: No, I mean I think it varies. There's a number of different circumstances where an individual is PCSing or is -- and somehow finds themselves unable to get the vaccine.

DR. OFFIT: I don't know what that acronym is.

DR. SCHECKELHOFF: I'm sorry. It's a permanent change of station, so especially folks that are traveling from OCONUS locations overseas back to --

DR. OFFIT: So just an administrative reason. Nothing --

DR. SCHECKELHOFF: I'm sure there are some individuals that are actively avoiding vaccination and they are --

DR. OFFIT: And they can do that? You can do that?

DR. SCHECKELHOFF: No, you should not be doing that.

DR. EL SAHLY: Dr. Meissner. Wiesen.

DR. WIESEN: Sorry. I can shed a little bit more light on how this works. So the vaccine program,

you know, we give the vaccine with everyone else and it's a commander's program. So the commanders are required to get all their folks vaccinated. But there is a distribution of who comes in first and who might come in later and how much energy you're going to put into trying to get everyone done.

And so the requirement is everybody gets vaccinated by June, right? And we have targets -- we want everybody vaccinated -- I think it's 90 percent by January 15 of the year of the flu or, you know, '18/19. It would've been '19 this year. But yeah, you could still get vaccinated later. Some people are coming into the service, so you entered the service after, you know, the vaccination program started. And so they've got to catch up with you.

But in the end, the commander's energy to try and track down every last person will eventually run out. There are medical exemptions and those people are -- how that was counted in this study, I don't know, but we track them. So we track exemptions, primarily in active duty. It has to be a medical exemption.

There are some rare administrative exemptions, but it's very infrequent.

DR. EL SAHLY: Meissner's turn.

DR. MEISSNER: Thank you. I thank you for a very clear presentation, a lot of information. It was interesting. So the first question is, does the influenza vaccine come from one manufacturer, or do you get vaccine from a number of different sources?

DR. SCHECKELHOFF: It was primarily from one manufacturer, this year.

DR. MEISSNER: And is it different in the Northern Hemisphere? It's a different vaccine that's used in the Southern Hemisphere than in the Northern Hemisphere, I assume?

DR. SCHECKELHOFF: So that's -- I don't know if you want to speak to this. That's currently up for discussion within DoD. Right now, it's a Northern Hemisphere vaccine. The Southern Hemisphere vaccine has not been distributed to active duty service members at this time, to my understanding.

DR. MEISSNER: And -- okay. Thank you. One

other comment: I noticed in the data that Lisa Grohskopf presented this morning, there was a notch in the amount of influenza activity at the end of 2018 and the start of 2019, which I think is oftentimes observed. But that also seemed to be present in African and Asian countries too.

And I've heard it attributed to the fact that people go home or they're no longer in college or -- and that it may be an epidemiologic factor. But the fact that it occurs apparently on a worldwide basis suggests that there's something else. I don't know if you or anyone has a comment to that.

DR. EL SAHLY: Okay. Well, we're going to take a -- yes, and we're running behind time so --

DR. JANES: I just wanted to respond to the question about the test-negative design. You know, I would totally agree that there's very limited information here in terms of VE with a very highly vaccinated population. Almost regardless of study design, any design that would assess overall incidents of flu in vaccinated versus unvaccinated groups would

have low power, and that's in part what you're saying here. Potentially any design that could exploit some temporal variation in terms of when the vaccine is administered to different individuals could provide some more information.

But I also had a basic question which is, how are the vaccination statuses determined for the three sets of data that you presented? Is any of it self-reported or is it all based on medical records?

DR. SCHECKELHOFF: For the active duty and the recruits, those are all in the records. For beneficiaries, I believe, it should all be captured in the record. There's that civilian population in the southwest border. I believe some of that might be self-report. But I believe for the other two groups, all that data should be captured in the record.

DR. EL SAHLY: Dr. Monto.

DR. MONTO: Just a question based on the explanation that the 90 some odd percent was what was achieved at the end of June. How is time used in the analysis? Because it should be two weeks, at least,

allowing two weeks post vaccination?

DR. SCHECKELHOFF: So the data that was presented here was adjusted by date. But, again, the vaccine distribution for DoD also begins in August. So the bulk of the folks that are getting -- that 90 percent is usually, I believe this year, they hit 90 percent in early November, I believe.

DR. EL SAHLY: Levine.

DR. LEVINE: Yeah. This is about medical exemptions. This would be a very rare instance, but I'm wondering what your -- what you do in this instance if there were an active service member who had a history of Guillain–Barré syndrome for whatever reason? Would they be exempt from all influenza vaccines or just from egg-based? What do y'all do?

DR. SCHECKELHOFF: I don't know. Sir, do you know the answer?

DR. WIESEN: So the medical exemptions, they're going to get a specialty evaluation first, and the recommendation of the allergist/immunologist is going to determine whether they get a medical exemption

or not. So, yeah, we would have the experts determine for the service members. So the primary thing is we're not going to put people at risk, but we don't want to give inappropriate exemptions when they're not warranted. But we defer that to the experts.

DR. SCHECKELHOFF: I mean, I will say that DoD did purchase limited amounts of the other formulations of the vaccine to cover medical exemptions. So, the thought being that if there was some reason to get them -- exempt them from the inactivated egg-based quadrivalent, that there would be another option, although, in much more limited quantity. But I don't know, again, based on the expert and on a case by case basis, how that would turn out.

DR. EL SAHLY: Okay. One last comment because we need to move.

DR. WIESEN: I know. I'll be quick. First, I had a question about the disclaimer, because my understanding is you're presenting the official DoD position. If that's not true and you're presenting your own personal opinion -- I'm just trying to figure

out -- because this should be an official position of the DoD. Is that correct?

DR. SCHECKELHOFF: When I put the slides through review at Armed Forces Health Surveillance Branch, that slide was included, so --

DR. WIESEN: Yeah, well, I assume that the committee members here are evaluating what you're presenting as the DoD position, so we'll get that clarified for the future.

And the only other point I wanted to make was that my understanding of what vaccine was purchased, procured by the DoD this year, is number one, we don't use a single manufacturer. We spread it out amongst all manufacturers. And that this year, we didn't produce anything other than the egg vaccine because there was no recommendation for the other formulations, and they were significantly more expensive. And so our procurement process basically says if there is no objective data to favor one versus the other, then you will purchase the product that is the most favorable to the government; in which case, egg-vaccine was

significantly cheaper. So that's my understanding.

You said that it was all -- I thought you said it was all recombinant or all -- I forgot what you said it was -- cell-based. But I don't think that's true. I would just want to double check on that to be sure. We are running -- there is an approved protocol that is going on now that's looking at the differences between those two -- actually, all three formulations, specifically; but it's so early, we have no information on that otherwise.

DR. EL SAHLY: Okay, thank you. Dr. Scheckelhoff for this very engaging discussion, and to the audience.

Next, Dr. Manju Joshi from CBER at the FDA is going to review the candidate vaccine strains and potency reagents.

CANDIDATE VACCINE STRAINS/POTENCY REAGENTS

DR. JOSHI: Good morning, everybody. I think I'm pretty much the last but one, I guess, in the session. I won't take much time, and try to keep it simple and quick.

I'm from Division of Biological Standards and Quality Control in Office of Compliance and Biologics Quality at CBER. Our division in collaboration with other essential regulatory laboratories participates in generation and calibration of reagents required for testing of influenza vaccine. Our division also manages and provides all these reagents to all the U.S. licensed manufacturers.

In my presentation, I will go over vaccines -- current candidate vaccine viruses and strains used in the current vaccine, as well as WHO recommendation for 2019/20 seasonal vaccine for trivalent and quadrivalent. I'll briefly mention the available reagents for each strain, and our division's goals towards preparing and supplying influenza vaccine testing reagents for the upcoming season.

This is more to the committee, but for the people in the audience up here, I'll make a few comments about planning for testing activities for the 2019/20 campaign and a couple of general comments, as always.

For influenza A(H1N1) type, the current vaccine strain was A/Michigan/45/2015-like virus. The list of different A/Michigan-live viruses and reassortants that were used in 2018/19 vaccine are listed here and, in the interest of time, I'm not going to read any of that.

WHO recommends a change of H1N1 strain for 2019/20 Northern Hemisphere campaign. The recommended strain is A/Brisbane/02/2018(H1N1)pdm09-like virus.

Currently, there are two available candidate vaccine viruses listed up here. Since there has been a strain change proposed, we know that inclusion of this strain in the vaccine is based on the decision made by the committee up here. But we have to consider the possibility that if it is recommended, what is going to be the status of the reagents?

We at CBER will work with other ERLs and manufacturers to prepare and calibrate the required reference antigen. Although the approval committee hasn't approved, but we've already started our work, initiated with production of antisera in that

direction.

Coming to the H3N2 strain, A/Singapore/INFIMH-like virus was used as H3N2 component in '18/'19 season. Here, there is a list of viruses which were used for egg-derived or cell-derived or for the recombinant vaccine. As all of us know today and we are still in the puzzle that WHO will announce a recommendation for H3N2 strain on 21st March. And once this strain is announced and CVVs are available, CBER will work with ERLs and manufacturers to prepare and calibrate the required reference antigen for egg, cell culture, and recombinant HA vaccines.

For the 2018/19 Northern Hemisphere campaign, WHO had recommended the B strain for trivalent and quadrivalent vaccine B, a B/Colorado-like virus from the B/Victoria lineage. The various viruses used in this year's vaccine included the B/Maryland and its reassortant for egg-based vaccine, B/Iowa for cell vaccine, and B/Maryland wild type for recombinant HA vaccine.

At this point, this season, the WHO has

recommended no change of B strain for Victoria lineage for 2019/20 campaign. And B/Colorado-like virus continues as the B strain in trivalent and quadrivalent vaccine. As far as a list of available candidate vaccine viruses are concerned, they can be obtained on the link I have provided at the bottom of the slide.

Today, if this strain is approved by the committee, we have to kind of look at it. What is the status of the reagent currently? Here in the table, I have laid out the reagents which were used by different -- for the current season. And at the same time, I'm pointing out what are the reagents available from CBER. So, as far as antisera reagent, which is always a concern, is we have sufficient supply of. Last year, we had manufacturers that used lot 1807, but currently, we do have -- we have prepared a new lot and lot 1810 is available. We are slightly low on one of the reference antigens for cell-based, but we are in process of preparing a replacement lot for it.

The quadrivalent vaccine, as all of us know, they are supposed to contain all the three vac strains

that are recommended for trivalent vaccine, plus an additional B strain from alternate B lineage, which is also referred to as second B strain.

For 2018/19, Northern Hemisphere campaign, WHO had recommended that the quadrivalent vaccine contain B/Puckett/3073/2013-like virus from the Yamagata lineage.

Again, as listed up here, B/Phuket wild type and its reassortant were used for egg-derived vaccine. B/Singapore/INFTT virus was used for the cell-based platform, and B/Phuket was also used for recombinant HA vaccine. Again, WHO has recommended no change for this B strain and B/Phuket from the Yamagata lineage will continue as a second B strain for '19/'20 campaign.

Again, there's a list of candidate vaccine virus available for this B strain and they can be obtained on the WHO website listed here.

Now let's go over the potency testing reagents for the strain. If this strain is approved at the committee today, the table here gives the list of available reagents. Most of them, which were used in

the previous season, they were prepared by CBER as well as by other ERLs.

And as far as CBER's situation is concerned, I will tell that we do have the new lots of antisera since our old lots were getting low. And we have already prepared a new antisera lot which is available. And one of the reagents for cell-based platform is running low, but we are already in the process of planning for a replacement of this.

Now coming to this was all to inform committee about the reagents and where we can be in terms of the testing of vaccine is concerned. But then this couple of next slides are going to be more for the manufacturers who are in the room and the users of the site ID reagents.

For smooth running of any campaign, it is very important to plan the things at the beginning of the season. And similar to the last year, the way we had done, we want manufacturers to provide certain information to our division for each strain used in the manufacturing. This should include as outlined up here

is the strain name, the reassortant or candidate vaccine virus they are planning to use, the reference antigen supplier and lot numbers, and the same for antiserum.

I hope all of you understand that this is extremely important for us to have this information to plan all our testing activity because this involves the planning for reagent calibration when new reagents are to be prepared. If you decide to use reagents from some other ERLs, we have to work towards importing those reagents in our domain; and those who deal with this, they already know that this itself is a complex process. So we want to be prepared ahead of time, so we don't cause any delay in testing.

Again, the first phase of testing from, as most everybody knows, is the monovalent testing, the recessive testing, that has to run smooth, and the lot release testing. And all of this have to be done in a timely manner. So we really request you to provide this information, so we can better plan it and run the campaign more smoothly.

Just coming down to some closing comments. Again, most of it is for the manufacturers and users of our reagents. Please note that only CBER-authorized reagents should be used to test the potency of vaccine marketed by the U.S. Please consult with us and let us know the reagents you're planning to use.

As the season starts, everybody is up and anxious to have their samples tested for the monovalents. We would like you to remember that please submit those samples to DBSQC. That's our division. Please email me regarding dispatch of test samples, test results, et cetera. And copy Dr. Shahabuddin and Dr. Eichelberger on these communications.

For any inquiries regarding CBER reagents standards, and reagents availability and shipping related issues, we have the CBER shipping request email. You can email there. I think most of you are familiar with this.

Another thing we would want you to know is that we would like to get any feedback or comments you have on the suitability of the -- or use of the

reagents provided, and any other aspects of our services. So we have a mailbox, the CBER influenza feedback, So please do send your comments or feedback and that will help us; and we can together work and improve the processes.

In closing, I want to emphasize that we at CBER are committed to making every effort to assure that reagents, appropriate for all strains for various platforms, are made available in a timely manner.

Again, as every year we do, this year again, we look forward to working together, as a team, with you here to achieve our goal of making vaccine available to the public in a timely manner. So again, we will start a new campaign together as a team and try to take it further and make it successful. Thank you all.

DR. EL SAHLY: Thank you, Dr. Joshi. Anyone have questions or comments? Dr. Meissner.

DR. MEISSNER: I may be the only one in the room that would ask this question; and if so, we can take it offline, but I don't understand. So each

season, there's a new influenza vaccine -- almost each season. And how does CBER evaluate each new vaccine from each manufacturer? What are the requirements to demonstrate an adequate immune response?

DR. JOSHI: Well, I think I would defer to Dr. Weir on that because every company sends their seed virus initially to -- and I think he would be able to better give you data.

DR. EL SAHLY: Okay. Dr. Weir.

DR. WEIR: We don't evaluate immune response every year. Once a manufacturer is licensed, and that's with an efficacy trial, then we evaluate their vaccines for potency using the standardized reagents. And so everyone has to have the standardized amount of so many micrograms of HA per mil.

DR. MEISSNER: Okay. Thank you.

DR. EL SAHLY: Additional questions to Dr. Joshi? Well, I thank you, Dr. Joshi.

The director of the Global Regulatory Affairs from GSK, Leslie Sands, will now provide the comment from the manufacturer.

COMMENT FROM THE MANUFACTURER

MS. SANDS: Good morning. Each year, CBER requests an annual summary of information from influenza vaccine manufacturers supplying the U.S. for purposes of a general presentation to the VRBPAC. This summary has been prepared from a variety of public sources and was reviewed by Sanofi Pasteur, AstraZeneca, Seqirus, Protein Sciences, and GSK.

In the chart to the left, you will see, since 1980, U.S. influenza vaccine supply has seen steady growth, year after year. During the 2017/18 season, greater than 90 percent of the vaccine supply was distributed. This can be seen in the graph on the right. Year after year, the number of doses being supplied is increasing. Yet, the window in which they are delivered is the same, which can be seen here in the chart on the right, about two months from the start of distribution; then supply starts to plateau.

So already on February 15, 2019, approximately 169.1 million doses have already been distributed in the 2018/2019 Northern Hemisphere season.

Manufacturers agree that in order to keep up with the demand for supply, we need well-matched strains, sufficient quantities, and timely preseason delivery.

This slide is a typical timeline of the annual influenza vaccine manufacturing supply of the Northern Hemisphere. For manufacturers, the last strain recommendation is key because it determines the level of risk based on the time to prepare working seed, optimize yields, and produce reagents. If the yield remains low, which has occurred as recently as 2006, then production time will be expected to be longer.

For the 2019/2020 Northern Hemisphere season, the WHO strain recommendation was February 21, 2019. During the announcement of the strain recommendation for the Northern Hemisphere, WHO postponed the recommendation for the A(H3N2) strain until March 21, 2019. Therefore, there will be a shift in the timeline. Production of strains will be later. And the start of vaccination will also shift due to manufacturers' ability to supply.

So, you can see on the timeline where it was

-- the initial decision was in February. Now it has moved to March 21, so towards the end of March. And now that will shift our production, as well as when vaccines will be available to the market and when vaccination actually starts. So now we are predicting that July will be the timeframe for when production can start, a formulation can start; and then, October, as to when vaccines will be available to the market.

There are a few critical factors related to influenza vaccine manufacturing. Global timing of strain selection to ensure the expected large vaccine volume is a key critical factor. Manufacturers need to be able to distribute and administer vaccine well before the peak season. And in order to accomplish this, candidate vaccine viruses and antigen yields from the least productive vaccine virus strain needs to be available to vaccine suppliers.

To ensure timely availability of the influenza vaccine, manufacturing of at least one strain starts at risk before the VRBPAC recommendations. This is shown on the timeline in the previous slide, starting in

January. Note that any deviation from WHO recommendations can impact timeliness and quantity of U.S. and global supply.

Industry believes that this is a partnership. And we appreciate the work that the WHO and national regulatory authorities are doing to ensure that the vaccines that we deliver will have the appropriate constellation of viruses to increase the level of protection the vaccines aim to provide. If timing is not consistently applied across the Northern Hemisphere regions, this can potentially impact vaccine availability.

This is an overview of the WHO 2019/2020 Northern Hemisphere season flu recommendation.

So, now since the announcement of the WHO 2019/20 Northern Hemisphere recommendation, manufacturing at risk could be delayed, which can impact supply due to the postponement of the strain selection for H3N2 by potentially delaying supply of volumes needed, especially if the new H3 strain has a low yield. If VRBPAC chooses a different H3 strain

from other global regions and/or WHO, in addition to the WHO H3 recommendation postponement, this will also impact vaccine supply as manufacturers accommodate supplying different products for different markets.

The availability of calibrated potency test reagents is an additional factor. Preparation and standardization of potency reagents for new strains is a complex process. Their availability is linked to global timing of strain selection for new strains and formulation can only start when calibrated reagents for the last strain are available. This is also seen in the timeline.

This slide here is a summary of how manufacturers have been preparing for the 2019/2020 season. So we have been tracking surveillance data through summaries of internal WHO teleconferences that include a table listing virus of interest. We've attended NIBSC meetings; participated in the annual BIO/FDA meeting, which took place in December 2018; and engaged in discussion with WHO Collaborating Centers.

We conduct regular reviews of websites such as

WHO; FluUpdate; and FluNet; CDC FluView; and GISAID, which is a key tool for vaccine supply and is regularly reviewed.

Manufacturers have been tracking availability of CVVs for manufacturing through WHO chaired technical teleconferences and updates from WHO Collaborating Centers that have been ongoing since the WHO Southern Hemisphere recommendation.

There's also a spreadsheet of viruses of interest and the stage of preparation of CVVs, which is now regularly shared with manufacturers providing timely updates on the development status. One challenge is that the spreadsheet, at times, does not reflect the current status of preparation and testing for release.

This is another timeline and it lists all of the meetings that industry is participating in throughout the year. So industry closely engages with WHO and U.S. agencies at multiple forms. This timeline illustrates sustained cooperation between WHO, U.S. agencies, and industry.

The complexities in the process of producing a seasonal influenza vaccine and the short timelines in which to achieve it, mean that it is critical that all stakeholders throughout the process coordinate activities and work together. There's a well-established professional cooperation between WHO; Global Influenza Surveillance and Response System, GISRS; and industry which facilitates the production and supply of well matched and therefore, more effective seasonal vaccines within the expected time frames.

This slide is a table of the principal egg-isolate CVVs that were evaluated for the Northern Hemisphere 2019/2020. The A strains are crossed out because those are the strains that were evaluated for egg-isolate prior to the recommendation in February by WHO.

These are the principal cell-isolates in this table that were evaluated for 2019/2020.

Next, I will provide an update on the Nagoya Protocol and provide some background and recent

examples of impact. The Nagoya Protocol was developed from access-and-benefit sharing discussions at the Convention on Biodiversity, adopted in 2010 and came into force in October 2014. The purpose was to ensure access to genetic resources and related traditional knowledge for potential use and to ensure users and providers of genetic resources and related traditional knowledge that they agree on fair and equitable sharing of benefits arising from their use. The benefits may be monetary or non-monetary.

In the past year, since the last time we presented, 12 additional countries have ratified the Nagoya Protocol, which now brings the total of countries that have ratified the Nagoya Protocol to 116 in total.

Seasonal influenza vaccine strain R&D is in scope of the Convention on Biodiversity/Nagoya Protocol, while pandemic appears exempt under Nagoya Protocol Article 4: Special International Instrument emergency response terms.

Pathogens are included; therefore, about three

months are required to formalize legal benefit sharing arrangements to the genetic resources from each source, Nagoya Protocol participating country.

Through 2019, industry will attend consultations and meetings with CBD, WHO and/or at the WHA to support Nagoya Protocol public health discussions to facilitate exempting influenza from Member State Nagoya Protocol legislation, impacting pathogen sharing and use, that significantly delay supply of vaccine to patients.

Manufacturers appreciate the efforts, but remain concerned about the impact to seasonal influenza vaccine supply for the U.S. market.

In the interest of time, I will not read through the examples of the Nagoya Protocol. I will just give some highlights. So, for the 2019/20 influenza vaccine, two strains originate from countries that have signed the Nagoya Protocol and reassortants are being prepared for both of them and they are listed below.

It's the A/Netherlands/10260/2018 which is an

H3N2, and A/Switzerland/3330/2017 which is H1N1. This is despite preexisting WHO terms of reference for national influenza centers to supply viruses to WHO Collaborating Centers.

This slide lists some additional examples. The result of delayed sharing of influenza vaccines or the CVVs derived from them could seriously challenge the timely supply of influenza vaccines with significant impact to national and global public health. This should be communicated to all countries.

Some countries, such as the Netherlands and the U.K., have waived the access benefit payments requirement for use of their genetic resources or have excluded pathogens from their national legislation. In the interest of public health, we strongly encourage other countries to do the same, either for existing or soon to be implemented Nagoya Protocol access benefit national legislation.

WHO is working on developing MTAs to formalize the terms of reference for the NICs, to supply virus to the WHO Collaborating Centers and include supply of

viruses to reassortant labs and manufacturers. However, at this stage, it is not clear if all countries will agree to the WHO's MTAs. Industry appreciates the hard work that the Francis Crick Institute and John McCauley of the WHO Collaborating Centers have put in to resolve the issues that have arisen as a result of the Nagoya Protocol.

To summarize our overall perspective, manufacturers are concerned about timely strain selection and agree that vaccine supply requires collaboration between multiple stakeholders to ensure sufficient provision of vaccine each season.

2019/2020 season manufacture preparedness is ongoing. However, there is the potential for delay in supply due to the postponement of the recommendation of the A(H3N2) strain. We agree that improvements need to be implemented to mitigate later strain recommendations.

Adherence to the Nagoya Protocol could result in a delay in influenza vaccine supply. The influenza vaccine industry is going to collaborate with WHO and

CBD to facilitate mitigating this risk. And lastly, we would like to emphasize the importance of maintaining public confidence in vaccination. Thank you.

DR. EL SAHLY: Thank you, Ms. Sands. Any questions for Ms. Sands? Yes, Dr. Kurilla.

DR. KURILLA: Just a clarification about Nagoya. It is not simply the pathogen, but the actual genetic sequence of the pathogen that is owned by the country which is the first one to report that particular sequence?

DR. EL SAHLY: Dr. Katz?

DR. KATZ: So right now, Nagoya Protocol covers -- it says genetic resources, but what is meant by that is actual physical material. There's ongoing discussion at the CBD as to whether genetic sequence information -- or they refer to it as digital sequence information, I think? But anyway, it's not explicitly covered under Nagoya right now, but they are -- there's ongoing discussions which will probably take several years to determine whether genetic sequence data itself would be included.

So right now, the issues related to Nagoya Protocol for the Collaborating Centers and GISRS, in general, is in actual virus sharing, the virus material itself.

DR. KURILLA: But if you were to take a sequence and make the virus, have you violated Nagoya? Because you now have the pathogen itself that sort of created the pathogen?

DR. KATZ: I'm not a lawyer, so I'm not going to speak to that. I mean, we can use reverse genetics and make candidate vaccine viruses. They're not exactly the wild type virus. I don't think that would be violating Nagoya.

DR. EL SAHLY: Dr. Meissner.

DR. MEISSNER: Do you have an approach for assessing the difference between vaccines, doses distributed, and actually administered? For example, you said there will be about 170 million doses of flus. Do you know how many of those -- or how do you estimate how many of those were actually administered?

MS. SANDS: Is anybody here from industry who

can answer that?

DR. EL SAHLY: Dr. Wharton alluded to 46 percent as of November, which brings it close to that number, doesn't it?

DR. WHARTON: So we do assess coverage through a variety of surveys and other methods over the course of the season. Notably, many of these rely on self-report and probably result in somewhat higher estimates than our -- reflecting some degree of confusion about probably what year the vaccine was received. But probably it's relatively consistent over time.

DR. EL SAHLY: Any additional questions to Ms. Sands? Okay. Thank you, Ms. Sands.

MS. SANDS: Thank you.

OPEN PUBLIC HEARING

DR. EL SAHLY: We'll move now to the open public hearing section of the meeting. Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor; its product; and if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

MS. HUNTER-THOMAS: Is there a Dr. Sam Lee present?

DR. LEE: Yes, hi. My name is Sam Lee. I'm with Sanofi Pasteur. I'm an employee of the company and fully supported by the company. I was going to make a comment, but in light of the decision to delay the consideration of the H3N2 strain selection today, I would withdraw my request for public comment. I will only say that I will support the comments of Ms. Sands earlier in that, you know, every week and every change from the typical process does add risk. And so risk of having enough vaccine, enough risk of having the vaccine at the right time in order to maximize vaccination rates. So I would just encourage that the decisions would be made as quickly as possible. Thank you.

DR. EL SAHLY: Thank you, Mr. Lee. Any questions? No. All right. Any other speakers?

MS. HUNTER-THOMAS: If there are no other public speakers, we'll proceed to the lunch break. We will reconvene at 12:40. Thank you.

LUNCH BREAK

CALL TO ORDER/THANK YOU DR. EDWARDS

DR. EL SAHLY: Well, good afternoon, everyone. So we'll reconvene now for the second portion of today's meeting. At the beginning of this portion, Dr. Marion Gruber from the FDA is going to present a something something for a little someone -- someone special.

DR. GRUBER: Good afternoon. Dear members of VRBPAC and FDA colleagues and members of the public, I would like to take a couple of minutes and thank Dr. Katherine Edwards for many, many years of service to this Vaccines and Related Biological Products Advisory Committee, not only as a member, but of note, as a chair for the past four years. I would like to thank her for the time and the expertise she has lent to the work of this committee.

Kathy, over the last four years as chair of this committee, you have guided this committee to provide advice, make recommendations, and vote on a wide range of very complex and sometimes very difficult topics that included but, of course, are not limited

to, making recommendations and voting on this strains to be included in the seasonal influenza vaccines for not only the Northern, but also the Southern Hemisphere vaccines. You have voted on the safety and the effectiveness of novel adjuvanted vaccines to protect against herpes zoster and hepatitis B.

Kathy, you have guided the committee in discussions on considerations for evaluating respiratory syncytial virus vaccine candidates in sera negative infants and provided your perspective on the safety and effectiveness of vaccines to be used in pregnant women to protect the young infant from infectious disease.

And last, but not least, you provided valuable input regarding site visit and numerous site visit reports pertaining to OVRR's mission critical research program.

So, Kathy, your advice, your experience, your wisdom, and most of all, your voice of reason really, really were most helpful to the work that the Office of Vaccines is doing to advance public health.

So, on behalf of the FDA, on behalf of CBER and OVRR, I want to express my appreciation and thank you for your valuable contributions, your time and effort, and your service to this committee. And I do have the honor to present you with this Advisory Committee Service Award signed by Dr. Marks, the CBER Center Director; and Dr. Gottlieb, the Commissioner of Food and Drug, at least as for now.

MS. HUNTER-THOMAS: Thank you so much, Dr. Gruber; and thank you again, Dr. Edwards, for your service to VRBPAC.

We're going to proceed with the committee discussion recommendations and vote now. Nick, if you could put up the slide with -- oh, he's already on it. Okay. And I'll hand the meeting back over to Dr. Edward -- I mean, Dr. El Sahly. Thank you.

COMMITTEE DISCUSSION/RECOMMENDATIONS/VOTE

DR. EL SAHLY: Okay, so the questions are up on the screen. And before we vote, would open the floor for comments, thoughts, questions, requests for clarifications on any of what was presented this

morning. We'll begin by reading the questions.

Question one: For the composition of the trivalent 2019/2020 influenza virus vaccine in the U.S., does the committee recommend: (a) the inclusion of an A/Brisbane/02/2018(H1N1) pandemic 09-like virus, (b) inclusion of a B/Colorado/06/2017-like virus B/Victoria? And for the quadrivalent 2019/2020 influenza vaccine in the U.S., does the committee recommend inclusion of the B/Phuket/3073/2013-like virus B/Yamagata lineage as the second influenza B strain in the vaccine?

Before we vote, I don't know if anyone has additional thoughts. Dr. Myron Levine.

DR. LEVINE: I'm a bit jet lagged, so I may have missed something this morning. But it seems to me that there are really three questions. And to answer them from this morning, do we know the status of the necessary reagents to allow an expeditious change to the composition? In other words, are all the necessary reagents available for each of those three? If somebody could just review that very quickly, that

might be helpful in terms of the vote?

DR. EL SAHLY: So Dr. Joshi was here this morning; but, Dr. Weir, you want to comment on it?

DR. WEIR: I will start on part of it. We have candidate vaccine strains available for all three and Manju can update about reagents.

DR. JOSHI: I think most of the reagents for B/Colorado and B/Phuket are available. And ERLs are working towards preparation of A/Brisbane/02 reagents because just the candidate virus became available. So that's a start of the process on that; but the other two strains, yes, the reagents or most of the things are available.

DR. EL SAHLY: Thank you, Dr. Joshi. Any final comments? Dr. Wharton.

DR. WHARTON: So I would be interested from some of the influenza experts here; to what degree the divergence we're seeing in H3N2 has recent precedent? And is this what we can expect in the future if we have -- as we try to maintain high coverage and have a population that hopefully is less susceptible to

influenza viruses? Will the viruses continue to diverge in these difficult and complex ways that will make it increasingly difficult to make decisions like this?

DR. EL SAHLY: There's one part of the question that's easy. Yes, it will continue to diverge in complex ways. And then the harder part of the question, Dr. Katz?

DR. KATZ: So I think we are in a period of for the H3N2s anyway of unprecedented diversity in the number of competing genetic subclades. And I'm not sure to what extent vaccination contributes, if at all. We see this genetic heterogeneity in places that don't vaccinate heavily, I mean, in other parts of the world. The balance of things is -- that's the other thing that seems to be unique now from season to season is we can't predict in a given region whether B's are going to predominate over A's in certain countries within the H1s and H3s. It's hard to predict that. And particularly within the H3s, we're also seeing now regional differences with the different genetic

subgroups.

So I'd say that, yes, there is an increase in complexity. And it's not just H3N2, as we've seen now with H1. And even the B/Victorias, the diversity there in terms of the double and triple deletions. I can't recall a time where we've seen three out of four the viruses being this diverse.

I think the more we can understand the consequences of population immunity, whether it's through natural infection or vaccination, I think that certainly is driving these viruses into this dynamic. And I think we need to get a better handle on that to really be able to better predict what's going to happen in the upcoming season.

DR. EL SAHLY: Okay. Thank you. Dr. Monto and then --

DR. MONTO: And who would have predicted that after two reasonably big -- one very big -- H3N2 years, we would see H3N2 showing up in the United States now becoming predominant in parts of the country where it wasn't predominant before? Because we always

say we don't predict flu and then we predict the -- try to predict flu. We said it was going to be an H1N1 year and here we've got H3N2. And B is coming in right now. The late B wave has started.

DR. KATZ: Thanks.

DR. EL SAHLY: Dr. Edwards.

DR. EDWARDS: Is this a function that it's really new, or that we have all these tools to be able to measure the changes? Do we know?

DR. KATZ: I think, I mean we've got more sequence data than ever before. So, things that may not have been that visible to us are very visible. And certainly, within the U.S. now, with our next generation sequencing and the approaches that CDC is put in place in terms of our sequence strategy and our -- we're also sampling the viruses for better representativeness. So even if viruses aren't circulating at very high frequencies, we can sample more and detect variants more readily.

I mean we put that process in place deliberately to see these things, to have a better idea

of what might be emerging. And so that no doubt contributes to the complexity. But I think, over and above that, it's also just the virus.

DR. EL SAHLY: Dr. Kurilla.

DR. KURILLA: Just out of curiosity, not something necessarily relevant for today's decision, but do we anticipate, or do we have a timeline as to when the trivalent would actually be discontinued and we would only use a quadrivalent version?

DR. KATZ: I think some of the vaccines for older adults are only in a trivalent form. Is that right, the high dose? It's probably a question for manufacturers. It's trivalent, right.

DR. EL SAHLY: Dr. Weir.

DR. WEIR: I think it will be market driven, to a great extent. I mean, if everyone wants quadrivalent, then manufacturers will quit making trivalents.

DR. EL SAHLY: Aren't we close to 80 percent quadrivalent now? Am I right? Dr. Bennink.

DR. BENNINK: Yeah, let me ask you, Jackie,

you know, in the past, we've sort of switched -- and this sort of doesn't address the triple deletion thing, but we sort of switched from one year to the other to go from Victoria lineage to Yamagata, and this year we're not switching. What was the thoughts behind that?

DR. KATZ: Well, overall, there was very little B activity this year, but the B activity we did see -- and, again, there was regional variation. But if you take the global picture, there was pretty much equal B/Vic and B/Yam. And it seemed like, again, in recent months since the beginning of the year, that was maybe turning a little bit more towards B/Vic than B/Yam. Also the B/Yams have just been out there, circulating at quite high levels for a number of years. So, again we just felt that it was better to keep the population vaccinated with the strain that they perhaps had not seen as much of which was the B/Victoria lineage.

DR. EL SAHLY: Dr. Janes.

DR. JANES: I wanted to comment on the vaccine

efficacy estimates, having seen them now for a couple of these meetings; and just reiterate some of the comments that have been made before about potential new ways that those data could be looked at, and complement the discussions of this committee. And in particular, looking at the DoD population and whether or not there's information to be exploited in terms of the timing of vaccination with regard -- or in relation to incident infection; particularly in light of recent data showing that the immune-responses wane quite rapidly.

So perhaps there's information to be gleaned in terms of efficacy and how that varies as a function of time since vaccination. And as well, exploiting the information that I understand exists on the vaccination history of the individuals in the DoD database; to the extent that informs on influence of immune responses by virtue of prior vaccination history. So whether or not those additional analyses would assist in the deliberations of this committee.

DR. EL SAHLY: Dr. Katz.

DR. KATZ: Just a point there that those types of things are looked at, particularly repeat vaccination, but also timing of vaccination and possible waning of VE. It's best done on the complete dataset that we get later on in the year. So, at this time, for the current season, it's very hard to get that data. But for earlier seasons, that data probably is available for past seasons. Yeah.

DR. EL SAHLY: Dr. Wiesen.

DR. WIESEN: Yeah, just to quickly respond to the question about, well, could DoD do some other stuff that we don't have? I think we could. I just want to point out that DoD research is just like everybody else's research. You know, everybody has to be consented. We can't just go and make you participate or comb through records looking for stuff.

So the same kind of problems that you have with recruiting into whether it's a cohort study or randomized controlled study, we have too; drop out, people moving, they lose interest, how do you pay them, all this other kind of stuff.

So I think we have information that we potentially could look at and I'll continue to work with our partners at the Defense Health Agency to see if we can shape the presentation that we give here to answer some of those kinds of aspects that DoD's uniquely positioned, potentially, to answer, because I don't want to repeat information you already have. I want to make good use of your time. But, yes, those are the kinds of things we could potentially look at.

DR. EL SAHLY: Thank you all. If there are no other comments, we will proceed with the vote on the three questions.

Question one: For the trivalent 2019/2020 influenza vaccine in the U.S., does the committee recommend inclusion of an A/Brisbane/02/2018(H1N1) pandemic 09-like virus? Please use your microphones and tools to vote.

MS. HUNTER-THOMAS: And, Dr. Beckham, I'll take your verbal vote, since you're on the line, of yes or no.

DR. BECKHAM: Yes.

MS. HUNTER-THOMAS: Okay. Thank you. I'll record it.

DR. EL SAHLY: Okay. It's up now. Place your vote now.

So for the first strain, the H1N1 pandemic 09, we had --

MS. HUNTER-THOMAS: Oh, individually? So it's a total of 14 votes and we have 14 yes. And the individual votes are as follows: Dr. El Sahly, yes; Dr. Beckham on the phone, yes; Dr. Swamy, yes; Dr. Wharton, yes; Dr. Bennink, yes; Dr. Edwards, yes; Dr. Wiesen, yes; Dr. Janes, yes; Dr. Kurilla, yes; Dr. Levine, yes; Dr. Meissner, yes; Dr. Monto, yes; Dr. Offit, yes; and Dr. Shane, yes. Thank you.

DR. EL SAHLY: Okay, moving on to the second strain for the trivalent 2019/2020 flu vaccine in the U.S. Does the committee recommend, yes or no, the inclusion of a B/Colorado/06/2017-like virus of the Victoria lineage?

MS. HUNTER-THOMAS: And, Dr. Beckham, I'll take your vote again verbal.

DR. BECKHAM: Yes.

MS. HUNTER-THOMAS: Thank you.

And again, for question number two, we have a total of 14 yes's, and zero no's. Reading again: Dr. El Sahly, yes; Dr. Beckham, yes; Dr. Swamy, yes; Dr. Wharton, yes; Dr. Bennink, yes; Dr. Edwards, yes; Dr. Wiesen, yes; Dr. Janes, yes; Dr. Kurilla, yes; Dr. Levine, yes; Dr. Meissner, yes; Dr. Monto, yes; Dr. Offit, yes; and Dr. Shane, yes. So a total of 14 yes votes. Thank you.

DR. EL SAHLY: And the third question for today, the quadrivalent 2019/2020 influenza vaccine in the U.S. Does the committee recommend the inclusion have a B/Phuket/3073/2013-like virus B/Yamagata lineage as the second influenza B strain in the vaccine?

MS. HUNTER-THOMAS: Dr. Beckham, I'm ready to take your vote verbal.

DR. BECKHAM: Yes.

MS. HUNTER-THOMAS: Thank you.

And, again, for the third question, we have a total of 14 yes votes, zero no votes. So I'll read

individually: Dr. El Sahly, yes; Dr. Beckham, yes; Dr. Swamy, yes; Dr. Wharton, yes; Dr. Bennink, yes; Dr. Edwards, yes; Dr. Wiesen, yes -- is it Wiesen or Wiesen? Wiesen, yes; Dr. Janes, yes; Dr. Kurilla, yes; Dr. Levine, yes; Dr. Meissner, yes; Dr. Monto, yes; Dr. Offit, yes; and Dr. Shane, yes. So 14 yes votes. Thank you.

DR. EL SAHLY: That concludes the first part of the day. Thank you all.

MS. HUNTER-THOMAS: So, since we are concluding topic one a bit early, we're going to take a longer break then. Maybe -- what do you say?

DR. EL SAHLY: I don't know. What do y'all want? 10, 15 minutes sound good?

MS. HUNTER-THOMAS: You want a 10-minute break or --

DR. EL SAHLY: Ten-minute break.

MS. HUNTER-THOMAS: -- or do you want a --

DR. EL SAHLY: Or longer? Whatever you want.

MS. HUNTER-THOMAS: You want to move on?

DR. EL SAHLY: Okay.

MS. HUNTER-THOMAS: Okay. We'll need to take a few minutes anyway because Dr. Carolyn Wilson needs to come. But in the meantime, I can go ahead and read the Conflict of Interest statement for topic two.

CONFLICT OF INTEREST STATEMENT

DR. EL SAHLY: So topic two today will be the presentation of the Laboratory of Retroviruses and Laboratory of Immunoregulation at the Division of Viral Products, Office of Vaccine Research and Review, Center for Biologics Evaluation and Research at the FDA.

MS. HUNTER-THOMAS: Okay, thank you, everyone. I will proceed to read the COI statement for topic two. The Food and Drug Administration is convening today, March 6, 2019, for the 155th Meeting of the Vaccines and Related Biological Products Advisory Committee, under the authority of the Federal Advisory Committee Act of 1972.

This afternoon for topic two, the VRBPAC committee will meet in open session to hear overview presentations on the intramural laboratory research programs of the Laboratory of Amino Regulation and the

Laboratory of Retroviruses. Per agency guidance, this session is determined to be a non-particular matter, which would have no impact on outside financial interests. Hence, no effective firms are identified, and members were not screened for this topic. Later this afternoon the meeting will be closed to permit discussion where disclosure would constitute a clearly unwarranted invasion of personal privacy, per 5 U.S. Code 552(b)(C)(6).

With the exception of the industry representative, all participants of the committee are special government employees, or regular federal government employees from other agencies, and are subject to the federal Conflict of Interest laws and regulations. This Conflict of Interest statement will be available for public viewing at the registration table.

Dr. Hendrik Nolte is currently serving as the acting industry representative to this committee. Dr. Nolte is employed by ALK, Inc. Industry representatives act on behalf of all related industry

and bring general industry perspective to the committee. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Hence, they do not participate in the closed sessions and do not have voting privileges.

Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee, and hence, do have voting privileges and they are authorized to participate in the closed session. This concludes my reading of the Conflict of Interest statement for the public record. And we are, at this time, have to take a momentary hold until Dr. Carolyn Wilson arrives. She should be on her way. Thank you.

DR. EL SAHLY: Okay, that will serve as the break, I guess.

BREAK

MS. HUNTER-THOMAS: Okay, everyone. We're going to reconvene. We have a plan of action now.

We're going to present out of order, but present who's here. Present with the presenters who's here, if that makes sense.

DR. EL SAHLY: In order to -- our first presenter for the topic two would have been Dr. Carolyn Wilson, but she will come later. So Dr. Jerry Weir is going to begin with an overview of the Division of the Viral Products of the FDA. Dr. Weir.

OVERVIEW OF DIVISION OF VIRAL PRODUCTS

DR. WEIR: Anybody know how to do this? I'm not sure how to advance the slides. Oh, okay. Sorry.

Okay, so I'm going to give a quick overview of the Division of Viral Products in the Office of Vaccines. And some of you have heard this a dozen times or more, so I'll try to be brief. It's sort of a hybrid Office of Vaccines Division of Viral Products talk or overview.

So, the Office of Vaccines Research and Review, which Marion Gruber is the director, has three divisions: the Division of Viral Products, which is ours; the Division of Bacterial, Parasitic, and

Allergenic Products; and a Division of Vaccines and Related Product Applications. The two on the left, Viral Products and Bacterial Products, are the product divisions that have a research component.

The OVRR Regulatory Mission and Portfolio is briefly to protect and enhance public health by assuring the availability of safe and effective vaccines, allergenic extracts, and other related products. So almost the majority of the products that we regulate are vaccines, but we also have allergenic products and diagnostic tests, live biotherapeutic products including FMT and phage therapy.

We have quite a few regulatory challenges that we have to face on a routine basis. One is, of course, because most of these are vaccines, is our emphasis on safety. Products are for mass use, often universal, and the recipients are often healthy individuals and often children.

There is -- like most product regulation at the FDA, there's a relatively short regulatory cycle. The example today, of course, is seasonal influenza

vaccines which is, of course, quite constrained in the time period that we have to act. We also react to and have to respond to emerging pathogens. Even in the last few years, Ebola, Zika, and of course pandemic vaccines.

Some of our products are quite old. Many of the legacy vaccines that still work very well, but there are new innovative technologies being utilized to improve these products. And over and above all of this, research plays a critical role in the regulation of vaccines.

Now, the research goals of the Office of Vaccines are threefold: safety, efficacy, and availability. All of our research is designed to meet one of these major goals: enhance the safety of preventative vaccines and related biological products through the development of models, methods, and reagents needed in the manufacture evaluation of these products; or efficacy, to improve the effectiveness of vaccines and related biological products through the development of models, methods, and reagents needed to

measure and predict the effectiveness of these products; and also we're concerned with availability, to develop and study approaches to enhance the availability of vaccines and related biological products.

Now I'll turn to the Division of Viral Products. Here we have seven laboratories, and these are laboratories that I like to think of with a large L. There's sometimes several laboratories within them. But the seven laboratories are arranged roughly, but not perfectly, along product lines that we regulate. The two labs in question today, or that you're getting a site visit report, are the Laboratory of Retroviruses, Hana Golding is the chief; and the Laboratory of Immunoregulation with Carol Weiss as the chief.

Now, for the Division of Viral Products, the mission and function is also quite simple; we regulate viral vaccines and related biological products, ensuring their safety and efficacy for human use. And similarly, we try to facilitate the development,

evaluation, and licensure of new viral vaccines that positively impact the public health.

Our major responsibilities include quite a few different aspects. One is the Investigational New Drug and Biologic License Application review and other pre-marketing activities. We're also heavily involved in BLA supplement review, lot release review, and other post-marketing activities.

The staff participate in manufacturer inspections, both pre- and post-licensure. We have an extensive role in consultation with other public health agencies including the WHO. And last but not least, we conduct research related to the development, manufacturing, evaluation, and testing of viral vaccines.

The role of research in the Division of Viral Products: All of our research and laboratory activities are designed to complement the regulatory mission. The laboratories address issues related to regulated viral vaccines, but they also try to anticipate and address issues related to the

development and evaluation of new viral vaccines.

Sometimes these are very general issues that are applicable to many products or product classes; for example, cell substrate issues. And sometimes the research and the laboratory work is focused on specific product issues; for example, correlates of protection necessary for efficacy evaluation or animal models that are necessary for animal rule implementation.

The next two slides -- I think it's two -- give you a quick snapshot of the staff and the budget of the division for the -- I have the data for the past year FY18. The division has 75 -- about 75 --full-time equivalents. These are government employees, but the staff is supplemented by approximately 40 different contractors. Most of these are through our ORISE program, but this program supports both post-doctoral fellows as well as post-bacc students.

Last year our division budget, which was pretty good. It was actually very good. We had a basic operating budget of $4.8 million. We had targeted FDA supportive another $1.4 million, and we

had external support of about $1.8 million. I will say that for actually several years in a row now, we've had quite a sufficient budget to do most of what we wanted to do.

The number of FTEs by laboratory. As I sort of alluded to a minute ago, all of the laboratories are not the same size. They have different numbers of principal investigators in them. This just shows you the number of FTEs in the different laboratories, as it's currently constituted.

The site visit evaluation that you're going to get the report from now is a program review to assess the progress on projects pursued since the previous site visit. In many cases, there will be an individual review component, different staff up for consideration for promotion. And as always, we ask the Site Visit Committee to comment and evaluate future directions because that's, of course, important to us, internally as well. And that's it.

DR. EL SAHLY: Thank you, Dr. Weiss. Anyone have questions for Dr. Weiss? I'm sorry, Dr. Weir.

Okay, with that I invite then Dr. Weiss to give her overview.

OVERVIEW OF LAB OF IMMUNOREGULATION

DR. WEISS: Okay. Good afternoon. I will be providing a very brief and high-level overview of the research activities in the Lab of Immunoregulation.

Okay, so the Lab of Immunoregulation has two research units. One is headed by Dr. Ira Berkower, and he has in his unit one staff fellow and, generally, two post-baccs or post-docs who are often supported by competitive funding. The other unit, I head. In my lab, I have one full-time permanent staff scientist, one staff fellow, one lab manager; and generally, one to three post-docs or post-baccs also tend to be supported by competitive funding.

So all of the PIs and all of the staff fellows are involved in regulatory review. And we provide expert scientific review of FDA submissions for experimental and licensed viral vaccines. The vast majority of our review work is involved in product or CMC review. That is all aspects related to the product

quality, purity, potency, and manufacturing consistency.

Dr. Berkower and I still also do a small bit of clinical review. This is for experimental HIV vaccines, especially therapeutic vaccines with complex protocols involving combination products and antiretroviral treatment interruptions. And we're also involved in some outreach activities with a variety of stakeholders.

Our review portfolio aligns with our research, and it includes responsibilities for all BLA and IND amendments for the licensed, cell-based inactivated influenza vaccine. We also review INDs for novel, seasonal, and pandemic influenza vaccines, and we've also participated in facilities inspections.

We also review INDs for experimental HIV vaccines. And this includes a wide array of products including inactivated HIV, recombinant proteins; single-cycle, replicating, and other novel vectors; usually in prime-boost combinations; and with complex protocols that are often used for these newer HIV cure

strategies.

We're also involved in our regulatory collaborations. So we're currently involved in interagency egg/cell serology working group. We're providing samples and sharing data for comparing assays for measuring neutralizing antibody titers and assessing the antigenicity of vaccine and emerging strains. We're also developing and characterizing monoclonals in collaboration with the Weir lab for the development of some new potency assays.

We've also contributed data in international consortiums to help with the development of standards and to compare assays for both influenza viruses and Ebola viruses. And as well, we often serve as FDA representative on various panels and workshops, and WHO consultations are an example.

So, our research actually really importantly provides us with the hands-on bench laboratory expertise that is needed for review of the types of products that we see in our applications. So we are making recombinant envelope proteins and characterizing

them; and this involves immunogen design, expression, and purification studies. We also need to know all the assays for antigenic characterization and stability and immunogenicity.

We also do a lot with neutralization studies for HIV and influenza. This involves both assay development and its applications. We do serology studies, and are looking for antibody correlates of protection after both infection and vaccination. We are also making broadly neutralizing antibodies and characterizing them, in particularly, to conserved regions of HIV and HA, such as in the stem, and trying to understand mechanisms of antibody.

We're also involved in vector design and characterization; and Dr. Berkower is using the live attenuated rubella virus as a model. These include studies about insert expression, immunogenicity, vector stability and safety, as well as durability and boosting of the immune responses.

So now just the next few slides, just highlights of the research going on in my laboratory.

So in my lab, we study virus entry and neutralization of HIV and influenza viruses. These viruses have common features for their entry mechanism; and so, many of our projects are really highly complementary.

So both glycoproteins spikes on HIV and influenza undergo major conformational changes during entry. They transition from a native prefusion conformation, on the left -- that's evolved in virus attachment -- and undergo a series of major conformational changes that lead up to membrane fusion that delivers the viral genome to the cell.

So both HIV envelope and HA influenza, in their native conformations or profusion conformations, are really metastable because they've evolved to undergo major conformation changes. They are both trimers, and it is these native or prefusion trimers that really are the targets of most of the neutralizing antibodies. The neutralizing antibodies inhibit both virus attachment, as well as the necessary conformational changes needed for fusion.

So when we think about vaccine antigens, it's

important that they have the proper conformation and that those conformations are actually stable, so they elicit the right antibodies.

So a brief slide on our HIV projects. So the approach we've been using is to generate a panel of envelope proteins from viruses that are selected for resistance to peptide fusion inhibitors that target very conserved regions in the envelope and some of the fusion intermediate conformations of envelope. This is helping us to identify not only the resistance mutations of potential new inhibitors but also gp120 and gp41 networks that confer resistance but yet work together to still maintain envelope function.

Major findings are that we've identified resistance mutations and mechanisms and compared differences between the X4 and the R5 classes of HIV-1 viruses. We've elucidated specific gp120-41 residues and regions that actually regulate these conformational changes and help stabilize the native prefusion conformation. And we've described two modes of opening of the prefusion on conformation, presumably as it goes

on to some of the more intermediate conformations.

Our influenza projects fall roughly into three areas, but they are highly integrated with each other. We are trying to understand HA stability, residues affecting the stability of the native conformation, as well as the effect of the M2 protein on HA during biosynthesis. And then more recently, we're finding an interesting association between HA stability and potentially sensitivity to neutralization by stem antibodies.

We're also looking at serology studies, especially we're looking at the breadth and the titers of neutralizing antibodies after infection or after vaccination, and some of the factors that affect that such as pre-existing immunity and prior year vaccination and age.

And finally, we're also trying to understand antibody correlates of protection using neutralizing antibodies. This is both in natural outbreak settings as well as in human challenge studies. And as we heard earlier, I think there's increasing interest in using

utilizing antibodies as potential correlates, at least for some vaccines. Some of these emerging H3N2 strains don't hemagglutinate well. And some of the newer vaccines that are being developed, like these universal vaccines are targeting antibodies to the HA stem and those antibodies will not hemagglutinate.

So some major findings from the studies. We've looked at the breadth of neutralizing antibody responses after vaccination with the seasonal inactivated influenza vaccine. This was done with leftover sera from an older NIH clinical trial. And some of our findings were that we found that IIV elicited heterologous neutralizing antibodies to pass strains not in the vaccine. There was probably evidence of back boosting, as well as advanced or future strains of H1N1 and H3 strains, which is probably evidence of cross-neutralizing antibodies. And as well, we even saw a bump in neutralizing antibodies to the H2N2 strain, but this happened only in individuals who had birth years that indicated they were likely infected early in life.

Children had higher seroconversion rates to both the homologous and heterologous strains in this study compared to adults. And half the subjects in our study had received the prior year vaccines, so we were able to look at that effect and saw that, in fact, as others had seen, we saw blunting of the responses in those that had prior year vaccine. But importantly, those responses were still boosted, and the end titers were still pretty high.

In HA stability studies, we found that the M2 proton ion channel activity helps prevent the H1N1 pandemic 09 HA from premature inactivation in the biosynthetic pathway. We also identified a residue pair in the head and the stem that stabilized this HA. And also for H5 HA, we looked at a whole panel and found an interesting association between the stability of that HA and neutralization sensitivity to stem antibodies.

We're also looking forward to studies about neutralizing antibody correlates of protection, and we had the opportunity to look at an H3N2 outbreak in the

military. And in brief, our findings were that the odds of an H3N2 infection decreased by 41 percent, with every 2-fold increase in neutralizing antibody titer. This was very highly significant. And as well the odds of H3N2 associated pneumonia decreased by 52 percent with every 2-fold increase in neutralizing antibody titer.

So next I'll briefly highlight some of the research in Dr. Berkower's lab. So Dr. Berkower is studying the rubella virus as a live attenuated vector for delivery of vaccine antigens. Work in their lab has shown that they have found an insertion site in the rubella genome that appears to be quite flexible. It accepts many inserts from any kind of antigens and fairly large inserts, even including the SIV gag. This replicating vector elicits potent antibody and T cell responses to the inserts, and it also induces mucosal immunity.

So, he is studying use of this vector as immunotherapy, and the model he's chosen is to look at SIV infection in the non-human primate model. And so

this would be again immunotherapy for treatment of an infected animal. And the goal is sustained viral suppression or eradication of the viral reservoir. And this aligns roughly with some of the big NIH initiative to promote HIV cure strategies or eradication.

And as many of you probably heard in the news, there's been an influx of energy for HIV cure since they announced the second patient who has been apparently cured of HIV, although this involved major chemotherapy and bone marrow transplantation. So the goal for the community is that, hopefully, we can achieve this with the safer methods, such as with immunotherapy and drugs.

So the approach he's using is to have acute SIV infection in the non-human primates. And then, several days after infection, treat with antiretroviral therapy, and this will suppress the virus growth and allow the immune system to take over. And it also limits the viral reservoir and it mimics neonatal infection. Immunizations take place during a suppression on antiretroviral therapy, and then

antiretroviral therapy will be withdrawn to determine if the immune response can limit viral rebound. And studies like this are going on in humans.

And so this is the results of that study. So again, there are three phases. There's the briefly infection phase, treatment with antiretroviral therapy with immunizations. The immunizations are two DNA vaccines and then two rubella vector vaccines delivering the gag insert. There are four animals in each group, a control group and the treatment group. And then, finally, the antiretroviral therapy is stopped so that we can measure viral rebound.

So, in the controls, he found that three of the four primates rapidly rebounded with a high level of viremia after the ART was stopped. And one of those progressed to the AIDS syndrome.

In the immunized group, one of four rebounded, but three of four sustained undetectable viral load through 24 months. So this is experiment number one and experiment confirmation is ongoing.

Major findings then are that rubella vectors

based on the vaccine strain are a safe and potent vaccine platform. Immunogenicity is comparable to the natural infection, including durability and boosting. You can boost with the rubella vector. It may have a role in immunotherapy, allowing ART withdrawal. And it importantly also permits many types of inserts; so not just HIV, but hepatitis C virus, malaria, and even cell surface antigens for creating new vectors.

Okay. With that, I'll stop for the sake of time. I have not included a large list of collaborators, including those in the division and CBER and outside of CBER. So thank you.

DR. EL SAHLY: Thank you, Dr. Weiss.

I'll begin with a question. Have the data on the rubella vector been published?

DR. WEISS: Some of the insert data has been published.

DR. EL SAHLY: What about the --

DR. WEISS: The monkey study. What's the status of that?

UNIDENTIFIED MALE: It's under internal

review.

DR. EL SAHLY: Internal review.

DR. WEISS: It's close to being submitted, I guess.

DR. EL SAHLY: Okay. Very good. Thank you.

Okay, thank you. So we'll go back to the top of the list now and we'll circle back to Dr. Wilson.

DR. WILSON: So, actually just to keep the momentum going on the science, if you want to go ahead with Dr. Golding and I'll just come in at the very end.

DR. EL SAHLY: Close at the end.

DR. WILSON: I do apologize to the chair and to the committee for being late.

DR. EL SAHLY: Okay. No problem.

DR. WILSON: I missed the messages.

DR. EL SAHLY: Okay. Dr. Hana Golding is going to do an overview of the lab of retrovirology.

OVERVIEW OF LABORATORY OF RETROVIRUSES

DR. GOLDING: It is my pleasure to share with you some of the activities in the Lab of Retroviruses in the last five years. And, indeed, it was a very

active five years. The Lab of Retroviruses is divided into two sections. In addition to being the lead chief, I'm also the head of the Unit of Viral Immunology and Pathogenesis. And I have two senior staff scientists, Dr. Marina Zaitseva and Dr. Surender Khurana, that are mentoring and leading multiple projects. And we have several research assistants: Jody Manischewitz, Tatiana Romantseva, and Lisa King.

And we have been successful in having six or seven post-doc and post-bacc during the last several years. Arifa Khan is the head of the Unit of Molecular Retrovirology. The other FTEs are Dr. Hailun Ma, a staff fellow; Dr. Belete Teferedegne had been with Dr. Khan but now moved on to the DVRPA, but she now has a new fellow, Andrea Erikna (phonetic), which started recently. And Dr. Sandra Fuentes is also a member of the lab, in addition to several post-docs and post-baccs.

Similar to what you heard from Dr. Weir and Dr. Weiss, we are in a constantly evolving landscape of infectious diseases. And specifically, we point out in

the last five years, we have severe outbreaks of Ebola, Zika virus, and multiple transmission of avian influenza viruses to humans with potential pandemic.

So how do we respond to this say ever-changing landscape? We believe that our goal is really to be very nimble and to facilitate rapid deployment of vaccines against emerging diseases. That includes sort of two 2-tiered approaches. One is to identify regulatory and scientific gaps in knowledge, methods of vaccine release, and correlates of protection. And some of the activities are by LR researcher-regulators provide expertise for review and reorient our scientific programs to address the challenges of new vaccines, including the use of new cell lines as vaccine cell substrate in manufacturing platforms, novel immunogen/adjuvant design, and new endpoints for clinical trials.

We developed advanced technology for improved analysis of safety of novel cell substrate, humoral immune responses post-infection and vaccination, adjuvant safety and mode of action, vaccine potency

assays, and various animal models for preclinical evaluation of vaccines including safety and effectiveness.

So, in the regulatory arena, we are covering very large classes of vaccines. The main portfolio includes HIV, influenza vaccines, as well as RSV, adjuvanted vaccines from multiple pathogens. Those include a different a type of production both non replicating and replicating virus vector, nucleic acid vaccine, live attenuated vaccine, and recombinant protein peptide-based vaccine.

As I indicated novel adjuvants and vaccine delivery system is very important; a large portfolio of our group. Universal influenza vaccines are now a very important part of it. And novel cell substrate and detection of an adventitious agent using next generation sequencing technologies, those include mammalian tumorigenic and tumor-derived cell lines, insect lines for baculovirus expression vectors, and avian cell lines.

We were involved in several important BLAs,

that were approved in the last five years, that I think will really sort of be a milestone. First was the Q-PAN-H5N1 which is an AS03 adjuvanted H5N1, a vaccine against H5N1 A/Indonesia; FLUAD MF59-adjuvanted seasonal influenza vaccine for the elderly; SHINGRIX, which is an AS01-adjuvanted VZV(gE) vaccine for the elderly; and earlier baculovirus-expressed recombinant trivalent HA proteins produced in Sf9 insect cells for persons more than 18 years old.

I would like to then describe in a little bit more detail their scientific project. So in my lab, as I indicated, I have two senior staff scientists that are really leading multiple projects. Dr. Zaitseva's focus is on adjuvant safety: mechanisms of production of pro-inflammatory mediators, both cytokines and prostaglandins E2, in human cell-based assay, which are predictive of in vivo reactogenicity. And she completed the series of studies in which you use bioluminescence imaging of live mice to understand the mechanism of protection against vaccinia challenge.

Dr. Khurana is leading several research

projects that include in-depth analysis of the humoral immune responses generated by different vaccine candidates versus infections, including influenza, RSV, Ebola, and Zika. Some of the new methods are whole genome phage display libraries and SPR technologies for antibody affinity measurement of polyclonal antibodies from both human and non-human primate.

Immunogen design and expressions against RSV and influenza with emphasis on the bacterial system, animal models for preclinical evaluation of vaccine candidate with emphasis on safety and effectiveness both of a new vaccine against influenza and RSV. Development of a new potency assay for, potentially, a rapid release of influenza vaccines. This is part of the large effort to shorten the timeline to release an influenza vaccine, both annually and in the face of a pandemic; new reporter-based neutralization assays, including against RSV; and more recently, universal influenza vaccine, evaluation of safety and efficacy.

Back to the studies of Dr. Marina Zaitseva, her goal was the development of in vitro assays using

human cell targets predictive of adjuvant toxicity in vivo. In way of introduction, we all know that adjuvants are included in vaccine formulation to activate antigen presenting cells. However, often or at least in some cases, strong activation of APC by adjuvant may induce excessive release of pyrogenic and inflammatory substances, causing adverse reaction in vaccine recipients. In animal models, a preclinical animal model may not always be predictive of safety of these novel adjuvants in humans.

Dr. Zaitseva identified an old adjuvant, muramyl dipeptide, that was already in the clinic in multiple clinical trials, actually of early clinical trials of HIV vaccine, and was associated with fever and reactogenicity, both in humans and in rabbits. And she used that as a prototype of reactogenic adjuvant to evaluate the values in vitro human cell-based assays.

More recently, she investigated the mechanism of production of prostaglandins E2, a proximal mediator of fever, as well as of pyrogenic cytokines including

IL-1 beta, IL-6, and IL-8 in human monocyte activated with MDP adjuvant. This led to an interesting finding that was somewhat unexpected that a T cell-derived GP1 beta alpha augment MDP induced pyrogenic responses and reactogenicity. Specifically, partially activated T cells that are purified by CD3 beads seems to shed the glycoprotein 1 beta alpha that binds to Mac-1 integrin on monocytes.

This T cell-derived GP1 beta alpha dramatically increased production of prostaglandin E2 and several pro-inflammatory cytokines in human monocytes activated with MDP. Blocking of the Mac-1 by antibodies in monocytes in vitro and experiments in Mac-1 knockout mice in vivo confirmed the role of Mac-1 in inflammatory responses to MDP.

So the novelty of this finding is that we described for the first time, the contribution of small peptide GP1 beta alpha that binds to Mac-1 signaling the production of pro-inflammatory substances in monocytes in response to MDP adjuvant.

Therefore, the outcome suggests that further

studies of T cell-monocyte nexus might help in the assessment of inflammatory potential of novel adjuvants. The in vitro based assays are valuable for down selection of novel adjuvant, and we already have transferred some of our assays to members of industry.

I would like to then shift to the studies led by Dr. Surender Khurana and remind us that there are multiple traditional assay used for vaccine responses; and they usually, in terms of the humoral response, include plaque reduction neutralization assays, or PRNT, hemagglutination inhibition assays, and various virus neutralization assay.

With Dr. Khurana was set up to do is to develop additional method that will provide additional insight about the quality and the repertoire, and the epitopes recognized by antibodies. Specifically, he developed the technology of whole genome fragments phage display library that gives a complete antibody epitope repertoire analysis and expanded the use of surface plasmon resonance to measure antibody kinetics, affinity maturation, and antibody isotype in polyclonal

sera.

In addition, he developed an animal model for evaluation of safety and efficacy of vaccine and therapeutics. And these tools were developed and applied in studies of human samples from influenza, RSV, Ebola, and Zika, both infections and vaccinations.

So what are the key accomplishments of Dr. Khurana in the various projects? With regards to RSV, the antigenic fingerprinting of RSV following primarily human infections in very young children, identified importance of anti-G antibodies, in addition to the MDF antibodies that have traditionally been followed.

Furthermore, Dr. Khurana went on to bacterially produce non-glycosylated G protein that was shown to actually be a safe and effective vaccine against RSV in mice and cotton rat challenge studies. And he published it in a series of papers and there is now interest including G as a possible component of future RSV vaccines.

In the area of influenza, there were multiple studies conducted both on avian influenza as well as

seasonal influenza. In the case of highly pathogenic H7N1 post-infection, Dr. Khurana identified evidence for anti-PA-X antibodies that have been postulated to play a pathogenic role, and indeed these sera included such antibodies following infection. He developed a high-throughput potency assay for rapid release of influenza vaccine, which is actually independent of the need for any antibodies or sheep sera.

He's done a lot of work to understand the added value of adjuvant to vaccines and show that adjuvant indeed improved not just the quantity but also the quality of antibodies. Expanded antibody repertoire against protective targets, or what we call epitope spreading, increased antibody affinity maturation, broader cross-protection against diverse avian influenza strain, and a similar finding was also found in several prime-boost protocols through collaboration with multiple groups.

In the case of universal vaccine, we are working on development of in vitro assays and animal models to better evaluate the potency, safety, and

effectiveness of different vaccine candidates, including the possibility of vaccine-associated enhanced respiratory disease.

In the areas of emerging disease, Zika virus, Dr. Khurana was able to obtain samples, both plasma and urine, from recent acute infection in Mexico, and he subjected them to whole genome immune profiling that revealed differential human IgG and IgM antibody repertoire in serum and urine. Also, antibody affinity to the Zika virus E protein inversely correlated with the disease severity at Day 28. And Zika virus serodiagnostic test based on several NS peptide identified by GFPDL are under development.

In the Ebola vaccination area, Dr. Khurana demonstrated the human antibody repertoire following VSV-Ebola, or DNA and protein vaccination, identified novel protective targets and the real importance of IgM antibodies in Ebola virus neutralization, especially during the early days post-vaccination and infection.

Strong correlation between anti-GP antibody's affinity and protection in Ebola virus animal challenge

studies were identified. And these types of studies led to the realization that both antibody affinity and durability are key parameters to be followed in ongoing and future Ebola virus vaccine studies.

I would like now to move to the program headed by Dr. Arifa Khan. She had two major projects: development of new technologies for investigating adventitious and endogenous viruses. That includes evaluation of next generation sequencing platforms for virus detection. That entailed method standardization, bioinformatics pipeline, development of reference material; and then investigation of endogenous and occult viruses in vaccine cell substrate, which is led by Dr. Hailun Ma, including Sf9 cells and Vero cells.

Project two is the development of in vitro and in vivo models for simian foamy virus infection in humans. The in vitro models for latent and active SFV infection include characterization of SFV-K3T in A549 cell clones, identification of biomarkers for SFV replication, identifying determinants of SFV fitness, and also analysis of SFV infection in naïve and

SIV-infected rhesus macaques to predict clinical outcome of humans infected with SFV, or co-infected with SFV and HIV.

Getting into the specific project, the NGS standardization for detection of known and novel adventitious agent for evaluating safety and cell substrates, vaccines and related biologics.

The accomplishments were very significant. The NGS potential for sensitive detection of adventitious viruses in complex biological samples was demonstrated by similar detection of four model viruses by three laboratories using independent sample preparation methods, different sequencing platforms, and bioinformatics pipeline. That required significant coordination and organization skill, I think, on the part of Dr. Khan and resulted in a publication in *mSphere*.

Five, well-characterized, large-scale reference virus stocks were developed for NGS standardization and are currently being used by some vaccine manufacturers. And a new reference virus

database was developed and is publicly available at the GWU HIVE and used by some vaccine sponsors.

This activity clearly has a regulatory impact. The availability of viral stocks for NGS standardization can facilitate its use for broad virus detection to evaluate safety biologics. NGS can enhance product safety by supplementing or replacing, ultimately, some current assays that have limitations for virus detection. And NGS laboratory effort is directly facilitating review of regulatory submission, which already includes NGS and development of regulatory guidance for using NGS for adventitious virus detection.

This approach was used specifically to look at Sf9 insect cells, which are used for the production of several vaccines, and there were several accomplishments. A novel rhabdovirus was actually detected using degenerate PCR and NGS by Dr. Hailun Ma and virus-negative and virus-positive cell clones were isolated from the ATCC Sf9 cell line. Infectivity assay for rhabdovirus was developed with the virus-

negative cell line. And cell clone with rhabdovirus variants in the X-gene were obtained and actually shown to be infectious. NGS analysis identified different families of endogenous retroelements that are being investigated to characterize the novel RT activity, which is constitutively produced from Sf9 cells, even though it's not been associated with infectivity so far.

The regulatory impact is that rhabdovirus discovery resulted in the establishment of PCR assays and viral clearance steps by manufacturers of baculovirus-expressed vaccines. Sf-rhabdovirus negative cell clone provides an important reagent for developing a sensitive assay for infectious virus detection. And a "clean" Sf9 cell line may be obtained for manufacturing and research purposes. Ongoing work to characterize the endogenous retroviruses activity in Sf9 will identify viruses with potential function to assess if they can pose any safety concern.

Lastly, the activity relationship regarding the foamy virus. The goal is to really develop in

vitro and in vivo models for simian foamy virus infections in humans. It includes identifying the viral and host determinants of SFV replication for assessing the potential of latent virus activation and clinical outcome in humans infected due to cross-species transmission from non-human primates.

There were several accomplishments in this project. Stable SFV-infected cell clones were obtained from infection of human A549 cells with a naturally occurring rhesus macaques SFV isolate. Clones were characterized for virus expression and particle production. And they identified several different types of clones. Some had latent, persistent, and chronic phenotypes were identified. Copy number was determined by PCR.

The virus rescue experiment indicated SFV latent infection was due to lack of early expression of the transactivated Tas gene. The RNA-Seq differentiate gene expression analysis suggests immune signaling pathways may be involved in SFV chronic infection.

Again, that may have a public health impact in

that SFV-A549 cell clones are a relevant model for natural virus infection in monkeys and possibly humans. Identification of markers for virus replication could help investigate latent virus activation and potential clinical outcome in human infections.

SFV-A549 cell clones provide useful research reagents to study the outcome of virus co-infections in humans that are exposed to different nonhuman primate species infected with different virus strain in natural or research setting. That's the end of my summary.

DR. EL SAHLY: Thank you, Dr. Golding. Any questions for Dr. Golding? Okay. Hearing none. Thank you.

We will circle back to Dr. Wilson, who will give the overview of the Division of Viral Products.

OVERVIEW OF RESEARCH/SITE VISIT PROCESS, CBER

DR. WILSON: Overview of the Center.

DR. EL SAHLY: Yes. Yes.

DR. WILSON: Okay. I know it's confusing coming at the end. Usually I am at the first, and that makes more sense to give an overview of the Center at

the beginning.

Again, I apologize for being late. Unfortunately, I missed the messages that the discussion went very quickly. So congratulations on finishing early, and I am glad that you pushed on and continued.

So, what I will do today is give you a quick overview of the Center and just provide a little bit more of the context for why we do the site visits and the other types of processes that we have in place to evaluate our research programs.

So the center regulates a variety of complex products. Obviously, you're very familiar with vaccines. You probably have become familiar with live biotherapeutic products, allergenic products that are also regulated by Office of Vaccines and the complexities associated with both of those categories as well.

In addition, we are responsible for the safety of the blood supply; regulate blood and blood components; blood derivatives; various related devices

that are associated with the blood industry but also with certain cell therapies as well, for example; gene therapies; as well as certain human tissues; and xenotransplantation products.

So it's a wide remit of products with a huge public health impact; and also, a lot of complexity. As you can imagine, these are not terminally sterilized products. They are not something you can shoot in an HPLC and know what this is. And sometimes we don't even know what are the most important characteristics to evaluate, for example, for lot release.

So that's one of the reasons why we feel that science is a very important partner in the regulation to advance product development. And years ago, I developed this graphic. I apologize for those of you who've been on this committee for a long time and have seen this a million times. But for those of you who haven't, I think it helps to articulate why we think research is so critical to our regulatory mission; and that is that everything really starts with a public health issue that drives development of a novel

product. But oftentimes, those novel products really pose regulatory challenges, especially when you're going into first-in-human studies. You may not have appropriate assays in place to know how to evaluate them. You may not even know what needs to be evaluated. You may need to develop reference materials for assays that can be used to evaluate those products. There may not be good non-clinical models.

And so that's where regulatory science really helps to start filling some of those scientific gaps through a combination of discovery science and targeted development and tools. In that way we have a more informed way of making regulatory policy and decision. And as we get better information and guidance to sponsors, they're in a better position to provide data that allows us to make those benefit-risk decisions.

And at the end of the day we hope that we have the shared goal of licensing a product, that's both safe and effective, to address that initial public health need. And of course, our mission doesn't end there, because it's critically important to continue

the post-market surveillance; as I'm sure all of you know, in the vaccine area, I don't need to tell you that.

So, again, the benefits of our research program are really to integrate research and review. Our research scientists are what are called researcher reviewers, which means that they not only do research of their own, but they also do all the regulatory activities of full-time reviewers, meaning that they review submissions, they go out on inspections, they write guidance documents, they present here at advisory committees, and so on.

In this way, by having a firm footing in both the regulatory arena and the research arena, it helps us to identify the grassroots, the most important questions to answer, and making sure we're using our resources to address the most important questions.

It also, as I said, the outcome of this research should foster rational policy and decisions based on sound science, law, and public health impact. It also helps us to prepare for future innovative

products and public health challenges. By having active members of the research community going out to their scientific and professional meetings, they're hearing about things that aren't yet within our doors but are likely to come and allows us to be proactive in preparing our regulatory approach to those types of products.

We develop tools and data that are available to all stakeholders. We encourage publication in peer-reviewed scientific journals in order to make sure that all stakeholders are aware of our findings and support the development of product classes.

So, unlike product developers who may be developing tools and methods that are specific to their products, we typically try to do this in a way that's more product neutral that would facilitate a whole class of products. Obviously, the research program enables us to recruit and retain highly trained scientist with the necessary expertise to review regulatory submissions.

Across the center, we have a variety of

applied technologies and certain analytical chemistry like NMR, mass spectrometry. We also have flow cytometry expertise, microarray, high throughput sequencing or next gen sequencing, and related bioinformatics and IT infrastructure to support that.

As you would imagine, a lot of microbiology, immunology, biochemistry and molecular biology, and cell and developmental biology. And more recently, we've also started programs in tissue engineering and microphysiologic systems. Epidemiology with meta-analysis of large healthcare databases is critically important to our work, as is biostatistics and bioinformatics.

As you know, it's now over four years ago that we moved here to the White Oak facility. It enabled us to be able to expand and grow core facilities to help support the research program. So we now have core facility programs and flow cytometry, confocal and electron microscopy, biotechnology including next gen sequencing and a variety of more traditional biotechnology supports, and the bioinformatics support

for data analysis and storage.

We also have a state-of-the-art vivarium with an imaging facility with MRI, digital X-ray, in vivo imaging system, ultrasound, and CT, and procedure rooms that support both BSL-2 and BSL-3 animal work, as well as a transgenic derivation facility.

We also have stood up in the last few years a CBER peer mentoring group. This is led by a more senior PI and open to all PIs. It's a monthly meeting, and a variety of issues have been discussed in those meetings. It's been found to be of great benefit to some of our younger scientists. We've looked into more formal mentoring programs. And we feel that for a fairly small scientific organization, we don't really have the depth of expertise to provide a more formal mentoring program that's being stood up and other places like NIH and academia. But we have found that this particular model is working very well for improving chances of success for our younger scientists.

We obviously don't do all this by ourselves.

We heavily invest in external collaborations, both formal and informal. This is data just showing that we collaborate across the United States, across the globe, and with a variety of different sectors.

So to come back to the research management process, we now have a Regulatory Science Council which provides governance by developing research goals and objectives, a research evaluation framework and criteria to measure scientific and regulatory impact, and also performs portfolio review of the research programs. Along with this higher-level oversight program, we also do an annual evaluation of the research program at the management level and complement that with internal and external peer review. And the external peer review is the site visit.

So the Regulatory Science Council developed four major research goals to advance the scientific basis for regulation and biologics human tissues and blood by first, developing and evaluating technology reagents and standards to inform and improve chemistry manufacturing and controls. Second, develop and

assessment nonclinical models and methods predictive of clinical performance with respect to toxicity and effectiveness. Third, improving clinical evaluation pre- and post-licensure through use of big data, innovative designs, and statistical, analytical, and modeling approaches. And then finally, preparing for future regulatory and public health challenges.

We have also developed an evaluation framework that is aligned in four major areas: mission relevance, dissemination, scientific impact, and unique contribution and regulatory practice. So the dissemination piece is really about making sure that our science is being published and presented at relevant scientific meetings. But the impact is more about the uptake of that information by the scientific community and regulated stakeholders.

And then what's unique to us -- different from NIH or academia or other government agencies -- is how are we integrating the output into regulatory practice? We've developed tools in the last year or two to help us really more deliberately capture that information.

It's something we've been doing all along, but we haven't had good tools to really capture that translation into the regulatory domain.

So, our research evaluation is, as I mentioned, through a combination of management review and peer review. The management review occurs on an annual basis at the project level through the research management chain. We also do horizon scanning at the center at the Regulatory Science Council. Also, the Regulatory Science Council asked each office to develop a programmatic review and present that to the Regulatory Science Council.

The peer review -- every project is reviewed once every four years by an internal peer review committee. It's reviewed at the programmatic level once every four years by an external peer review; that's our site visit. And then we also have internal peer review, which is the committee for promotion and evaluation of researcher reviewers. This is more around certain personnel actions. And that's at the PI level.

So the site visit, again, is really the nexus for researcher reviewers, whether they're in a temporary position, like a senior staff fellow or staff fellow or whether they're permanent investigators, principal investigators, or staff scientists. The top two are independent scientists who get independent resources allocated to them by their division, and then staff fellows and staff scientists are support scientists to principal investigators.

So, to come to your report, the site visits are convened as subcommittees to the advisory committee. And, in the case of today, I want to especially thank Dr. Edwards and Dr. Monto who stood up as co-chairs for this particular review, which as you can imagine from hearing the overview presentations was quite a large group, quite a large body of work. So I really appreciate their leadership in this review.

So, the site visit team develops a report, which is a draft report, and then comes to this body, which has the opportunity to review it. Either they accept the report as written, amend the report, or

reject it, and send it back to the site visit team. And then once it's approved, it's a really valuable document. It's used by the CPERR, the internal peer review for supporting personnel actions that may be nominated by the division; by the PIs for improving their research programs -- they really take all of the scientific input very seriously; and by management for resource allocation decisions that may be impacted by the report.

So, finally, I'd like to thank all of you here today as well, again, as the committee that worked under Drs. Monto and Edwards for their time and effort to participate in the review and for you today for evaluating the review. I'm happy to answer any questions or happy to turn this back over to the chair and let you get on to business.

DR. EL SAHLY: Questions for Dr. Wilson?

DR. WILSON: Okay, thank you.

DR. EL SAHLY: Thank you, Dr. Wilson.

MS. HUNTER-THOMAS: Okay, so we're going to proceed with the closed session. And all parties that

are not involved -- thank you, Dr. Bennink, for your time. Thank you, Dr. Beckham, for your time today and, Colonel Wiesen, thank you. We'll take a few minutes.

OPEN MEETING ADJOURNED