

**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**

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1                   **CALL TO ORDER/INTRODUCTIONS**

2                   **DR. EL SAHLY:** Good morning, everyone. It's  
3 8:05. I would like to get started.

4                   Well, I want to welcome all of you to the  
5 155th meeting of the Vaccines and Related Biological  
6 Products Advisory Committee on this very cold March  
7 morning. I want to welcome the people in the room, as  
8 well as the individuals dialing in via the webcast. We  
9 will begin by introducing the committee members. Each  
10 member to introduce themselves, their institutional  
11 affiliation, and expertise.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 **DR. LEVINE:** Mike Levine.

8 **DR. MEISSNER:** Jumping right over me.

9 **DR. LEVINE:** Sorry.

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

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

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

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

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

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

7 **ADMIN ANNOUNCEMENTS, COI STATEMENT**

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

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

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

1 press could stand up so that everyone can identify you.

2 Is Paul here or Megan? Hi, Paul. Thank you for

3 coming. And then we do have a transcriptionist here.

4 Her name is Linda Giles. Thank you, Linda.

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

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

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



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

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

13 In the latter part of the afternoon, the  
14 meeting will be closed to permit discussions where  
15 disclosure would constitute a clearly unwarranted  
16 invasion of personal privacy, per 5 U.S. Code  
17 552(b)(c)(6). Related to the discussions at this  
18 meeting, all members and SGE consultants of this  
19 committee have been screened for potential financial  
20 conflict of interest of their own, as well as those  
21 imputed to them, including those of their spouse or

1 minor children, and for the purpose of 18 U.S. Code  
2 208, their employers. These interests may include  
3 investments, consulting, expert witness testimony,  
4 contracts and grants, CRADAs, speaking, teaching,  
5 writing, patents and royalties, and primary employment.

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

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

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

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

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

1 temporary non-voting member for topic one.

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

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

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

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

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

11 **INTRODUCTION**

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

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

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

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

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

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

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

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

21           Another challenge is the timeline for

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

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

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



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

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

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

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

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

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

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

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

1 Northern Hemisphere influenza seasons: an  
2 A/Brisbane/02/2018(H1N1)pdm09-like virus. They  
3 recommended to make a change from last year's  
4 recommendations A/Michigan/45/2015. For the B strain,  
5 they recommended a B/Colorado/06/2017-like virus from a  
6 Victoria lineage, which has no change from the 2018 and  
7 '19 recommendations. For the H3N2 strain, the  
8 recommendations will be announced on the 21st of March  
9 2019.

10           So, they also recommended the quadrivalent  
11 vaccines, which is supposed to contain two influenza B  
12 viruses, will contain the above virus and also a  
13 B/Phuket/3073/2013-like virus, which is from the  
14 B/Yamagata lineage. And there is no change from the  
15 2018 and '19 Northern Hemisphere recommendations. As  
16 in the previous years, the national or the regional  
17 control authority approved the composition and the  
18 formulation of vaccines used in each country.

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

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

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

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

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

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

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

1 inclusion of B/Phuket/3073/2013-like virus from the  
2 Yamagata lineage, or recommend an alternative candidate  
3 vaccine virus from the B/Yamagata lineage, or recommend  
4 a candidate vaccine virus from the B/Victoria lineage.

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

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

10 **U.S. SURVEILLANCE**

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

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

21 So first U.S. influenza surveillance.

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

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

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

1 viruses and do lineage determinations on Bs.

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

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

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



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

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

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

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

1 the -- or the figure, rather, on the right. This is a  
2 map that shows ILI activity by state. This is just a  
3 snapshot for Week 8. The change from Week 8 over Week  
4 7 was that during Week 7 there were 30 states plus New  
5 York City recording high activity, and then for Week 8,  
6 we had 33. So an increase of three states, plus New  
7 York City still there.

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

18           The overall rate as of Week 8 is 32.1 per  
19 100,000. Just for comparison, for last season 2017/18,  
20 Week 8, the cumulative rate was 84 per 100,000, so 84  
21 versus 32 per 100,000.

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

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

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

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

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

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

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

8           So, in summary, influenza activity remains  
9 elevated in the U.S. for this season. Influenza  
10 A(H1N1)pdm09 viruses have predominated overall for the  
11 whole U.S., but H3N2 viruses were detected more  
12 commonly than H1N1 viruses in the southeast and during  
13 Week 8 predominated nationally. An increasing  
14 proportion of the H3N2 viruses belong to the 3C.3a  
15 genetic group, which is antigenically distinct from the  
16 3C.2a genetic group. And, of course, as mentioned  
17 earlier, we're seeing, so far, very low proportions of  
18 influenza B viruses this season.

19           So moving on to a little bit about the interim  
20 2018/19 VE estimates. These come from the U.S. Flu VE  
21 Network. This map just points out where the sites that

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

6           A brief bit on methods. Enrollees are  
7 outpatients, aged 6 months or older with acute  
8 respiratory illness with cough for no more than seven  
9 days. Dates of enrollment for the data that I'm going  
10 to present are November 23, 2018, through February 2,  
11 2019. The design is a test-negative case-controlled  
12 design, which involves comparing vaccination odds among  
13 the influenza RT-PCR positive cases with the RT-PCR  
14 negative controls.

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

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

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

6           So results: Again, these are preliminary.  
7 The season's still ongoing, and we look forward to  
8 future data as more come in. In total, 3,254 were  
9 enrolled as of February 2 at the 5 sites. 465 or 14  
10 percent were RT-PCR positive for influenza. 2,789 or  
11 86 percent were negative. Looking at the 465  
12 positives, we have another pie chart which examines the  
13 makeup of that group. The majority is more or less --  
14 is very similar actually to the graph that we looked in  
15 U.S. surveillance. The majority of the viruses  
16 represented for (H1N1)pdm09, but we do also have some  
17 H3N2 in red. It's difficult to see the way this slide  
18 displays but Bs are, again, in the minority;  
19 B/Victorian and B/Yamagata each represent about one  
20 percent.

21           This graph summarizes the number of enrolled

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

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



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

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

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

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

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

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

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

19           **DR. EL SAHLY:** Thank you, Dr. Grohskopf. Dr.  
20 Edwards.

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

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

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

15 **DR. EL SAHLY:** Dr. Bennink.

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

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

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

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

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

5 **DR. EL SAHLY:** Dr. Kurilla?

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

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

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

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

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

10           **DR. EL SAHLY:** Dr. Meissner and then Dr.  
11 Monto. Sorry.

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

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

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

5 **DR. EL SAHLY:** Dr. Monto.

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

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

1 the vaccine.

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

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

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

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

21 **DR. WHARTON:** So we did publish early season



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

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

12 **DR. GROHSKOPF:** Thank you.

13 **WORLD SURVEILLANCE/VIRUS CHARACTERIZATION**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21           So in addition to these changes, which

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

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

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

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

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

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

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

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

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



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

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

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

1 previously that sometimes we could see differences with  
2 human sera. So we took some individual pediatric sera  
3 from children that had been vaccinated with the current  
4 2018/2019 season. We had a couple of age groups, and  
5 I'll show more of this data in a moment of our entire  
6 panels, but these were just some individual sera that  
7 we chose because they had good postvaccination titers.

8           You can see here, if we're looking now at the  
9 top, and then -- I don't know that this is going to  
10 show it either. Ah, yeah. Okay. So, if we look at  
11 the titers against the Michigan/45 reference viruses  
12 and then look down the columns, we can see that in many  
13 cases we're seeing at least a 4-fold if not an 8- or  
14 16-fold reduction in responses to some of the newly  
15 circulating viruses in this genetic group, the 6B.1A  
16 with a 183P. And some of these reductions are as high  
17 as what we see with a known antigenically variant virus  
18 that contains the 156 substitution. These viruses are  
19 in the minority; very few of them are in circulation.  
20 But, as I mentioned, these are predominating.

21           Okay. So, to wrap up our analysis for the

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

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

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

1 significant reduction compared to the response to the  
2 vaccine virus.

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

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

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

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

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

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

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

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

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

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

8           So, during this period, the data we had at the  
9 time of the vaccine consultation meeting was that the  
10 135K viruses were predominating. But overall these  
11 viruses are really recognized as a group antigenically,  
12 as you'll see in a moment. Then, we have 2a2 viruses  
13 and as you can see that's a smaller group. However,  
14 down below we have the 3a viruses, and I just want to  
15 make a note that these -- you may remember the 3a  
16 viruses from when they first emerged back in '13/'14  
17 when we had -- and 2014 onwards -- when we had that  
18 substantial antigenic drift that was comprised of both  
19 2a and 3a viruses. And in the 2015/16 season, we  
20 actually had a 3a vaccine component, the  
21 Switzerland/2013. But since that time these 3a's have

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

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

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



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

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

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

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

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

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

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

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

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

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

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

1 the response to antisera raised to cell-propagated  
2 Singapore/2016. And you can see the majority of  
3 viruses tested are well inhibited and a lower  
4 proportion are poorly inhibited. And at least the CDC  
5 data here, the vast majority of these viruses were the  
6 3a antigen or genetically variant viruses; so  
7 indicating that they are also antigenic variants as  
8 well as genetic variants.

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

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

21           We used this particular reference virus in our

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

6           So, this really just demonstrates again that  
7 we have test viruses here that belong to either the  
8 2a1b the group, the 2a2 or the 3a viruses. And the 2a2  
9 and 2a1b viruses are generally well inhibited by  
10 antisera raised to the cell-propagated Singapore  
11 antisera, not so well against the egg. And the 3a  
12 viruses are poorly inhibited by either sera and stand  
13 out from the 2a1b and 2a2 viruses.

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

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

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

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

1 vaccine in the U.S. this season.

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

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

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

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

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



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

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

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

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

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

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

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

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

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

1 numbers in this current period.

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

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

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

1 continents.

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

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

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

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

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

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

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

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

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

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

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

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

21           Again, the neuraminidase, some genetic



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

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

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

21           This is just summarized again. Again, we see

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

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

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

1 their proportions did vary.

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

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

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

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

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

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

1 branch at CDC. His team generates all of this data for  
2 CDC. And he will be taking over at the collaborating  
3 center, and so the person that you will be seeing here  
4 one year from now. So I will be on the call on the  
5 22nd, but after that, I wish you well. Thank you. So,  
6 any questions?

7 **DR. EL SAHLY:** Dr. Edwards.

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

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

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

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

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

16           **DR. EL SAHLY:** Dr. Bennink.

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

1 that is really nice actually to see.

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

8           **DR. KATZ:** Are you talking about these?

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

11          **DR. KATZ:** Right. Right.

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

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

15          **DR. BENNINK:** I didn't see a cartology either  
16 --

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

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

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

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

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

13 **DR. KATZ:** Hang on.

14 **DR. BENNINK:** Keep going. There.

15 **DR. KATZ:** Yeah. These are all --

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

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



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

4 **DR. BENNINK:** Okay.

5 **DR. KATZ:** Yeah.

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

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

20 **DR. EL SAHLY:** Dr. Weir.

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

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

7 **DR. EL SAHLY:** Dr. Monto.

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

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

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

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

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

14           **DR. EL SAHLY:** Yes. Here.

15           **DR. KATZ:** Right here.

16           **DR. EL SAHLY:** Yeah.

17           **DR. KATZ:** Okay.

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

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

5           **DR. EL SAHLY:** Double deletion egg.

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

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

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

11          **DR. EL SAHLY:** Ah, okay.

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

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

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

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

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

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

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

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

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

4 **DR. MONTO:** You do look at them.

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

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

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

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

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

5                                   **DoD VACCINE EFFECTIVENESS REPORT**

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

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

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

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

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

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



1 our geographic combatant commands within the DoD.

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

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

1 but we certainly have a fairly wide footprint.

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

9 Very similar to the other data that you've  
10 seen, on the graph to the left, the left axis is the  
11 number of specimens by week on the bottom axis and  
12 then the percent positives on the right-hand side. The  
13 different colors are indicative of the different  
14 subtypes of influenza. We're showing back from the  
15 2016/2017 season all the way through approximately  
16 about Week 4/Week 5.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 Then Asia data, the data we got from Asia,

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

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

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



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

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

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

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

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

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

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

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

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

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

21           I'll just note that the February data lack of

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

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

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

16           But, again, very similar to what's already  
17 been discussed, we're looking primarily at the V1A-  
18 2Del clade, which is this group here. Those are  
19 primarily, again, from North America. We have seen  
20 some of the emergence of the three deletion viruses.  
21 I'll caveat that by saying, if you look here on the

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

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

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

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

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

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

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

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

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

18           For the H3N2, obviously, this emergence of the  
19 3C.3a clade is interesting and needs to be taken into  
20 consideration. So, again, that's postponed until later  
21 this month. For the B/Victoria component, the

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

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

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



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

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

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

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

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

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

1           Interestingly, when you start breaking it out  
2 by subtypes of either H1 or H3N2, you see this; our  
3 highest VE estimates are for children with the H1N1 at  
4 66 percent. The adults were significant, but they had  
5 a much broader confidence interval. So not quite as  
6 strong there. And when you look at the H3N2, the one  
7 number that actually wasn't significant was this group  
8 of children. Again, the point estimate is suggestive  
9 of protection, but it was not significant. Whereas,  
10 the adult population that was observed in this group,  
11 also had a very high VE of 67 percent, which was pretty  
12 dramatic.

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

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

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

6           Again, crude and age-adjusted VE will be  
7 presented. We had 251 cases. These were all confirmed  
8 by real time PCR on a little over 1,100 controls. And  
9 the vaccination rates, again, are demonstrated there.  
10 Cases was about 13 percent and control is a little over  
11 25 percent. This -- I apologize. This is actually a  
12 typo of the prevalence -- was 91 percent H1, and H3 was  
13 only 8.4 percent. And as you see, we didn't have any  
14 influenza B in this population.

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

1           The data for the VE estimates for this  
2 population: because the number of H3N2 were so low, we  
3 adjusted influenza A overall, and then broke out H1N1  
4 separately. These estimations, again, whether you look  
5 at overall, zero to 17 years, 18 to 64 years, or over  
6 65 years, we had significant protection in all groups  
7 except for the 65 and over age group. This is, I'm  
8 guessing, primarily because the sample numbers for this  
9 group are so low, again, you see the point estimate is  
10 relatively good, but the confidence interval is very  
11 wide, so we're not able to make any statistical  
12 significance statements regarding those.

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

10           **DR. SCHECKELHOFF:** I'm certainly open to  
11 suggestions.

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

14           **DR. WIESEN:** I just have a separate question.

15           **DR. EL SAHLY:** Oh, separate.

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

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

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

13           **DR. EL SAHLY:** Dr. Offit and then Dr.  
14 Meissner.

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

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

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

6           **DR. SCHECKELHOFF:** I'm sorry. It's a  
7 permanent change of station, so especially folks that  
8 are traveling from OCONUS locations overseas back to  
9 --

10          **DR. OFFIT:** So just an administrative reason.  
11 Nothing --

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

15          **DR. OFFIT:** And they can do that? You can do  
16 that?

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

19          **DR. EL SAHLY:** Dr. Meissner. Wiesen.

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

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

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

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

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

3 **DR. EL SAHLY:** Meissner's turn.

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

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

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

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

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

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

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

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

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



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

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

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

17 **DR. EL SAHLY:** Dr. Monto.

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

1 allowing two weeks post vaccination?

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

8 **DR. EL SAHLY:** Levine.

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

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

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

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

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

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

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

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

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

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

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

1 significantly cheaper. So that's my understanding.

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

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

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

17           **CANDIDATE VACCINE STRAINS/POTENCY REAGENTS**

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

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

9 In my presentation, I will go over vaccines --  
10 current candidate vaccine viruses and strains used in  
11 the current vaccine, as well as WHO recommendation for  
12 2019/20 seasonal vaccine for trivalent and  
13 quadrivalent. I'll briefly mention the available  
14 reagents for each strain, and our division's goals  
15 towards preparing and supplying influenza vaccine  
16 testing reagents for the upcoming season.

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

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

7           WHO recommends a change of H1N1 strain for  
8 2019/20 Northern Hemisphere campaign. The recommended  
9 strain is A/Brisbane/02/2018(H1N1)pdm09-like virus.

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

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

1 direction.

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

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

21           At this point, this season, the WHO has



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 **DR. EL SAHLY:** Okay. Dr. Weir.

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

16 **DR. MEISSNER:** Okay. Thank you.

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

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

1   **COMMENT FROM THE MANUFACTURER**

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

9                   In the chart to the left, you will see, since  
10 1980, U.S. influenza vaccine supply has seen steady  
11 growth, year after year. During the 2017/18 season,  
12 greater than 90 percent of the vaccine supply was  
13 distributed. This can be seen in the graph on the  
14 right. Year after year, the number of doses being  
15 supplied is increasing. Yet, the window in which they  
16 are delivered is the same, which can be seen here in  
17 the chart on the right, about two months from the start  
18 of distribution; then supply starts to plateau.

19                   So already on February 15, 2019, approximately  
20 169.1 million doses have already been distributed in  
21 the 2018/2019 Northern Hemisphere season.



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

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

12           For the 2019/2020 Northern Hemisphere season,  
13 the WHO strain recommendation was February 21, 2019.  
14 During the announcement of the strain recommendation  
15 for the Northern Hemisphere, WHO postponed the  
16 recommendation for the A(H3N2) strain until March 21,  
17 2019. Therefore, there will be a shift in the  
18 timeline. Production of strains will be later. And  
19 the start of vaccination will also shift due to  
20 manufacturers' ability to supply.

21           So, you can see on the timeline where it was

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

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

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

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

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

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

15           So, now since the announcement of the WHO  
16 2019/20 Northern Hemisphere recommendation,  
17 manufacturing at risk could be delayed, which can  
18 impact supply due to the postponement of the strain  
19 selection for H3N2 by potentially delaying supply of  
20 volumes needed, especially if the new H3 strain has a  
21 low yield. If VRBPAC chooses a different H3 strain

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

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

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

21           We conduct regular reviews of websites such as

1 WHO; FluUpdate; and FluNet; CDC FluView; and GISAIID,  
2 which is a key tool for vaccine supply and is regularly  
3 reviewed.

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

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

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

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

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

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

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

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

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

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

21 Pathogens are included; therefore, about three

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

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

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

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

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



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

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

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

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

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

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

13           2019/2020 season manufacture preparedness is  
14 ongoing. However, there is the potential for delay in  
15 supply due to the postponement of the recommendation of  
16 the A(H3N2) strain. We agree that improvements need to  
17 be implemented to mitigate later strain  
18 recommendations.

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

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

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

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

11 **DR. EL SAHLY:** Dr. Katz?

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

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

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

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

14           **DR. EL SAHLY:** Dr. Meissner.

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

21           **MS. SANDS:** Is anybody here from industry who

1 can answer that?

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

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

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

14 **MS. SANDS:** Thank you.

15 **OPEN PUBLIC HEARING**

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

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

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

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

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

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

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

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

20

**LUNCH BREAK**

1                                   **CALL TO ORDER/THANK YOU DR. EDWARDS**

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

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

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



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

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

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

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

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

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

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

17           **COMMITTEE DISCUSSION/RECOMMENDATIONS/VOTE**

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

1 morning. We'll begin by reading the questions.

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

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

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

1 might be helpful in terms of the vote?

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

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

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

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

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

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

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

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

1 subgroups.

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

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

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

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

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

5 **DR. KATZ:** Thanks.

6 **DR. EL SAHLY:** Dr. Edwards.

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

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

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

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

4 **DR. EL SAHLY:** Dr. Kurilla.

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

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

14 **DR. EL SAHLY:** Dr. Weir.

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

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

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



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

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

20 **DR. EL SAHLY:** Dr. Janes.

21 **DR. JANES:** I wanted to comment on the vaccine

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

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

21           **DR. EL SAHLY:** Dr. Katz.

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

9           **DR. EL SAHLY:** Dr. Wiesen.

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

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

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

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

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

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

21           **DR. BECKHAM:** Yes.

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

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

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

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

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

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

1           **DR. BECKHAM:** Yes.

2           **MS. HUNTER-THOMAS:** Thank you.

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

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

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

18           **DR. BECKHAM:** Yes.

19           **MS. HUNTER-THOMAS:** Thank you.

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

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

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

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

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

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

17 **DR. EL SAHLY:** Ten-minute break.

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

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

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

21 **DR. EL SAHLY:** Okay.

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

5                                   **CONFLICT OF INTEREST STATEMENT**

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

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

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



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

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

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

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

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

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

19 **BREAK**

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

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

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

9                           **OVERVIEW OF DIVISION OF VIRAL PRODUCTS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 development and evaluation of new viral vaccines.

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

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

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



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

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

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

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

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

3 **OVERVIEW OF LAB OF IMMUNOREGULATION**

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

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

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

1 quality, purity, potency, and manufacturing  
2 consistency.

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

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

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

1 strategies.

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

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

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

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

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

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

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

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

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

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

21           So when we think about vaccine antigens, it's

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

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

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

1 on to some of the more intermediate conformations.

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21           Major findings then are that rubella vectors

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

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

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

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

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

18           **DR. EL SAHLY:** What about the --

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

21           **UNIDENTIFIED MALE:** It's under internal

1 review.

2 **DR. EL SAHLY:** Internal review.

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

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

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

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

11 **DR. EL SAHLY:** Close at the end.

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

14 **DR. EL SAHLY:** Okay. No problem.

15 **DR. WILSON:** I missed the messages.

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

18 **OVERVIEW OF LABORATORY OF RETROVIRUSES**

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

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

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

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



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

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

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

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

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

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

21           We were involved in several important BLAs,

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

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

21 Dr. Khurana is leading several research

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

8           Immunogen design and expressions against RSV  
9 and influenza with emphasis on the bacterial system,  
10 animal models for preclinical evaluation of vaccine  
11 candidate with emphasis on safety and effectiveness  
12 both of a new vaccine against influenza and RSV.  
13 Development of a new potency assay for, potentially, a  
14 rapid release of influenza vaccines. This is part of  
15 the large effort to shorten the timeline to release an  
16 influenza vaccine, both annually and in the face of a  
17 pandemic; new reporter-based neutralization assays,  
18 including against RSV; and more recently, universal  
19 influenza vaccine, evaluation of safety and efficacy.  
20           Back to the studies of Dr. Marina Zaitseva,  
21 her goal was the development of in vitro assays using

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

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

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

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

9           This T cell-derived GP1 beta alpha  
10 dramatically increased production of prostaglandin E2  
11 and several pro-inflammatory cytokines in human  
12 monocytes activated with MDP. Blocking of the Mac-1 by  
13 antibodies in monocytes in vitro and experiments in  
14 Mac-1 knockout mice in vivo confirmed the role of Mac-  
15 1 in inflammatory responses to MDP.

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

21           Therefore, the outcome suggests that further

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

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

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

1 sera.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21           Again, that may have a public health impact in

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

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

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

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

16 **OVERVIEW OF RESEARCH/SITE VISIT PROCESS, CBER**

17 **DR. WILSON:** Overview of the Center.

18 **DR. EL SAHLY:** Yes. Yes.

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



1 the beginning.

2           Again, I apologize for being late.

3 Unfortunately, I missed the messages that the  
4 discussion went very quickly. So congratulations on  
5 finishing early, and I am glad that you pushed on and  
6 continued.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21           Across the center, we have a variety of

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

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

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

1 for data analysis and storage.

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

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

21 We obviously don't do all this by ourselves.

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

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

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



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

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

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

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

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

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

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

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

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

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

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

17           **DR. EL SAHLY:** Questions for Dr. Wilson?

18           **DR. WILSON:** Okay, thank you.

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

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

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

4

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**OPEN MEETING ADJOURNED**