Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)

Vaccines and Related Biological

Products Advisory Committee

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This transcript appears as received from the commercial
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to typographical and factual errors recommended by the DFO.

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1   **PROCEEDINGS   (8:30 a.m.)**

2   **Agenda Item: Welcome**

3   DR. EDWARDS: Good morning. My name is Dr. Kathy

4   Edwards from Vanderbilt University, and I am very pleased

5   to chair the meeting this morning of the 145th meeting of

6   the VRBPAC. Today our goal will be to arrive at influenza

7   vaccine strains as we will go forward. I would like to

8   start, first of all, by also welcoming the public, but also

9   welcoming our participants and also the audience on the

10   webcast.

11   I'd like to start with Dr. Weir and if he could

12   introduce himself and we'll go around the table and with

13   our names and our affiliations.

14   DR. WEIR: I am Jerry Weir. I am the director of

15   the Division of Viral Products at CBER.

16   DR. KRAUSE: I am Phil Krause, deputy director of

17   the Office of Vaccines. Also, presenting, for Marion

18   Gruber, who is the director, who can't be here today.

19   DR. JANES: Good morning. I am Holly Janes. I am

20   a biostatistician. I am at the Fred Hutchinson Cancer

21   Research Center.

22   DR. EL SAHLY: Hana El Sahly, Baylor College of

23   Medicine. Vaccine Treatment and Evaluation Unit.

24   DR. ATREYA: Prabhakara Atreya, acting designated

25   federal officer for the Advisory Committee meeting. I am

1 also the director for the Division of Scientific Advisors &

2 Consultants.

3   DR. MOORE: Patrick Moore from the University of

4 Pittsburgh, Cancer Virology Program.

5   DR. MONTO: Arnold Monto, University of Michigan,

6 School of Public Health.

7   DR. WHARTON: Melinda Wharton, Immunization

8 Services Division, Centers for Disease Control and

9 Prevention.

10   DR. BENNINK: Jack Bennink, viral immunologist,

11 from NIAID, NIH.

12   DR. STANEK: Scott Stanek, preventive medicine.

13 Physician assigned to the Assistant Secretary of Defense

14 for Health Affairs, Health Readiness Policy and Oversight.

15   DR. SCOTT: Cherise Scott, director, Special

16 Programs at the Global Alliance for TB Drug Development.

17 Also known as TB Alliance.

18   DR. GREENBERG: David Greenberg, University of

19 Pittsburgh, School of Medicine and medical affairs, Sanofi

20 Pasteur. I am the industry representative.

21   DR. KATZ: Jackie Katz, deputy director of the

22 Influenza Division at CDC and also the director of the WHO

23 Collaborating Center for Surveillance, Epidemiology, and

24 Control of Influenza at CDC.

1   DR. EDWARDS: Dr. McInnes, would you catch your

2 breath and introduce yourself?

3   DR. MCINNES: Thank you, Dr. Edwards. Good

4 morning. Pamela McInnes, deputy director, National Center

5 for Advancing Translational Sciences at the NIH.

6   DR. EDWARDS: Thank you. Welcome, everyone. We

7 would like to now have the conflict of interest statement

8 read.

9   **Agenda Item: Conflict of Interest Statement**

10   DR. ATREYA: Good morning. I am Prabhakara

11 Atreya. As I mentioned, I'm the acting designated federal

12 officer for today's Vaccines and Related Biological

13 Products Advisory Committee. I would like to introduce my

14 colleagues, and also make some administrative remarks

15 before reading the conflict of interest statement for the

16 public record.

17   I would like to introduce our new DFO, Captain

18 Hunter Thomas, who will be in charge of VRBPAC for all the

19 future meetings, and you met Rosanna Harvey, the committee

20 management specialist for the VRBPAC, and also supported by

21 Denise Royster, assisting the meeting today, and we also

22 have our colleague Jeanette Devine, who is the conflict of

23 interest statement preparation and screening officer.

24   On behalf of FDA/CBER/VRBPAC, we would like to

25 welcome you all for the 145th VRBPAC meeting. Today's

1 session has one topic that was open to the public in its

2 entirety, the meeting topic is announced in the Federal

3 Registry Notice of January 12, 2017. Members that are

4 participating in person, public is attending in person or

5 watching the live webcast, the FDA CBER media contact is

6 Mr. Paul Richards who is in the audience. If you have any

7 questions with regards to press, he will be available.

8   And our transcriptionist is Chanda Chhay at the

9 meeting. He is going to be recording all the deliberations

10 and discussions.

11   I just wanted to mention that when you speak,

12 please press the microphone to talk and switch them off

13 when you have finished speaking. Please speak clearly and

14 loudly into the microphone so that the transcriptionist,

15 the members, public, and those listening via webcast can

16 hear the discussion.

17   We have an open public hearing session set aside

18 later in the day. OPH speakers, please sign your name and

19 affiliation on the form on the outside the registration

20 table so that we can announce you when the session comes.

21   And now I will read the conflict of interest

22 statement for the public record. The Food and Drug

23 Administration is convening today March 9, 2017, for the

24 145th meeting of the Vaccines and Related Biological

25 Products Advisory Committee under the authority of Federal

1   Advisory Committee Act of 1972. At this meeting, the

2   committee will discuss and make recommendations on the

3   strains to be included in the trivalent and quadrivalent

4   influenza virus vaccines for the 2017-2018 influenza

5   season.

6   The following information on the status of this

7   advisory committee's compliance with federal ethics and

8   conflict of interest laws including but not limited to 18

9   U.S. Code 208 is being provided to the participants at this

10   meeting and to the public. This conflict of interest

11   statement will be available for review at the registration

12   table.

13   With the exception of the industry

14   representative, all participants of the committee as

15   special government employees are regular federal employees

16   from other agencies and are subjected to federal conflict

17   of interest laws and regulations. Related to the

18   discussions at this meeting, members and consultants of

19   this committee have been screened for potential financial

20   conflicts of interest of their own as well as those imputed

21   to them, including those of their spouse or minor children

22   and for the purpose of 18 U.S. Code 208 their employers.

23   These interests may include investments, consulting, expert

24   witness testimony, contracts, grants, CRADAs, teaching,

1 speaking, writing, patents, royalties, and primary

2 employment.

3   FDA has determined that all members of this

4 advisory committee are in compliance with federal ethics

5 and conflicts of interest laws and that 18 U.S. Code 208,

6 Congress has authorized FDA to grant waivers to special

7 government employees and our regular government employees

8 who have a financial conflict of interest when it is

9 determined that the agency's need of a particular

10 individual's expertise and service outweighs his or her

11 potential financial conflicts of interest.

12   However, based on today's agenda and all

13 financial interests reported by members and consultants, no

14 conflicts of interest waivers were issued under 18 U.S.

15 Code 208. Dr. David Greenberg is currently serving as the

16 industry representative to this committee. Dr. Greenberg

17 is employed by Sanofi Pasteur U.S.

18   Industry representatives act on behalf of all

19 related industry and bring general industry perspective to

20 the committee. Industry representatives are not special

21 government employees and are not screened and do not vote

22 and do not participate in any closed sessions.

23   Dr. Cherise Scott is serving as the temporary

24 consumer representative to this committee at this meeting.

25 She is appointed as a special government employee and is a

1 temporary voting member who will bring consumer perspective

2 to the committee. Consumer representatives are screened

3 for their financial conflicts of interest and are cleared

4 prior to their participation.

5   At this meeting, there may be regulated industry

6 speakers and other outside organization speakers making

7 presentations. These speakers may have financial interests

8 associated with their employer and with other regulated

9 firms. The FDA asks in the interest of fairness that they

10 address the unique current or previous financial interests,

11 financial involvement with any firms whose products they

12 may wish to comment upon. These individuals were not

13 screened by the FDA for conflicts of interest.

14   FDA encourages all other participants to advise

15 the committee of any financial relationships that they may

16 have with any firms whose products are known as direct

17 competitors. We would like to remind members, consultants,

18 and participants that if the discussions involve any other

19 products or firms not already on the agenda for which an

20 FDA participant has a personal or imputed financial

21 interest, the participants need to exclude themselves from

22 such involvement and their exclusion will be noted for the

23 record.

24   This concludes my reading of the conflicts of

25 interest statement for the public record. Thank you.

1   DR. EDWARDS: Thank you very much, Dr. Atreya. We

2 will now begin our presentations. The first presentation

3 will be by Anissa Cheung, regulatory coordinator of the

4 division of viral products at CBER, and she will introduce

5 the topic.

6   **Topic: Strain Selection for the Influenza Virus**

7 **Vaccines for the 2017-2018 Influenza Season**

8   **Agenda Item: Introduction**

9   MS. CHEUNG: Good morning. I am going to

10 introduce the topics of today's VRBPAC meeting, the

11 influenza virus vaccines strain selections for the 2017-

12 2018 influenza season.

13   So the purpose of today's VRBPAC meeting is to

14 review the influenza surveillance and epidemiology data,

15 the antigenic characteristic of recent virus isolates,

16 serological responses to current vaccines, and the

17 availability of candidate vaccines strains and reagents,

18 and after the committee reviewed the data and at the end of

19 the discussions, the committee will be asked to make

20 recommendations for the strain of influenza A, both H1N1

21 and H3N2, and the B viruses to be included in the 2017 and

22 2018 influenza vaccines licensed for use in the United

23 States.

24   You are going to hear several presentations from

25 CDC and also DoD, and colleagues from CDC will present the

1 epidemiology of the circulating strains and this will

2 include surveillance data from both U.S. and around the

3 world. You will also hear talks on the antigenic

4 relationships among contemporary viruses and candidate

5 vaccine strains, and the types of assays and also the

6 techniques you are going to hear about include

7 hemagglutination inhibition test using post-infection

8 ferret serum and also the hemagglutination inhibition test

9 using panels of sera from humans receiving recent

10 inactivated influenza vaccines. Also, the virus

11 neutralization test, antigenic cartography, phylogenetic

12 analysis of HA and also NA genes, as well as the vaccine

13 effectiveness.

14   So there are several key challenges for vaccine

15 strain selections. First of all, vaccine effectiveness

16 really depends on the match between the hemagglutinins of

17 the vaccines also the HA of the circulating strain of

18 viruses, and as you know, the antigenic drift of HA is

19 continuous for both the influenza A and influenza B

20 viruses. However, the antibody of hemagglutinin correlated

21 with vaccines efficacy, and another challenge is the

22 timelines for influenza vaccines productions. The

23 timelines are relatively fixed and usually we have the

24 strain selections in late February or early March. It is

1 necessary in order to have the vaccines to be available for

2 the subsequent northern hemisphere winter season.

3   So normally the manufacturer have to begin

4 production of one monovalent strain before the strain

5 selections at risk in order to fulfill the timeframe. Also

6 the available of the reference strain which we also called

7 candidate vaccine virus, which needs to be suitable for

8 vaccine manufacturing. So what it means is the vaccine

9 productions heavily depends on the growth characteristic of

10 the strain used for manufacture.

11   So if the strain is not growing, you know, in the

12 optimal conditions with enough yield, it will be very

13 difficult, for them, for the manufacturer to grow. And

14 also the strain specific reagents needed for potency

15 determinations is very critical for the potency

16 determinations for both the inactivated and the recombinant

17 protein vaccines.

18   So I would like to give you a pictorial

19 illustration of the seasonal influenza vaccines production

20 timetable, and you can see starting from the first steps

21 strain selections and then the generation of the reference

22 viruses and the productions of the potency reagent. As you

23 can see, they are all, all the activities are back to back,

24 and any delays of the above steps will have a big impact on

1 the distributions of the influenza vaccines to the public

2 prior to the influenza seasons.

3   And the working viruses for the productions of

4 the inactivated influenza vaccines are traditionally

5 isolated from eggs, and the antigenicity are characterized

6 by the WHO collaborating centers. Starting in August 31,

7 2016, the use of MDCK cell isolated candidate vaccine

8 strain was approved for the manufacturer of the Flucelvax

9 monovalent bulk.

10   This cell-derived candidate vaccine virus strain

11 is manufacturer-specific and it is derived from two

12 approved WHO collaborating centers. However, the antigenic

13 analysis is performed the same way as performed for the

14 isolated vaccine virus strain. Last of all, the working

15 viruses are approved for quality and safety by the national

16 regulatory authorities.

17   For the influenza B virus strain, we know that

18 there are two antigenically distinct lineages are always

19 cocirculating in each seasons, and they are represented by

20 B/Victoria/287 and also B/Yamagata/1688, and right now we

21 have both the trivalent and quadrivalent influenza vaccines

22 available in the United States, and currently we have seven

23 quadrivalent influenza vaccines being licensed in the

24 United States.

1   The current process for selecting appropriate B

2   strain for inclusion in the trivalent and quadrivalent

3   vaccines is similar to the procedure that we use over the

4   years for the trivalent vaccines recommendations. The WHO

5   and the VRBPAC committee will review the data and make

6   recommendations for each formulations, the trivalent and

7   also the quadrivalent.

8   So I would like to have a quick review of the

9   previous recommendations for the 2016-2017 northern

10   hemisphere influenza virus strain compositions. So a

11   little bit a year ago, on March 4, 2016, we have the VRBPAC

12   strain selections meeting, and at that time the committee

13   recommended the following strain for inclusion in the U.S.

14   2016-2017 trivalent influenza vaccines. For the H1N1

15   strain, they recommend A/California/7/2009 H1N1 pdm09-like

16   virus, and there is no change from the 2015-2016 northern

17   hemisphere recommendations.

18   For the H3N2 strain, they recommended A/Hong

19   Kong/4801/2014 H3N2-like virus. There is a change from the

20   A/Switzerland/9714293/2013 H3N2-like virus vaccines, but

21   same as the 2016 southern hemisphere recommendations.

22   For the B strain, they recommend the

23   B/Brisbane/60/2008-like viruses, which is from B/Victoria

24   lineage, and there is a change from the B/Phuket/3073/2013-

1   like virus, which is from the B/Yamagata lineage, but the

2   same as 2016 southern hemisphere recommendations.

3   For manufacturers producing a quadrivalent

4   vaccine, the committee recommended a second B strain, which

5   is a B/Phuket/3073/2013-like virus from B/Yamagata, and

6   this strain previously recommended for quadrivalent

7   vaccines in 2016 southern hemisphere.

8   Also, we have another VRBPAC on October 13, 2016,

9   and this is the first VRBPAC for the recommendations for

10 influenza vaccines for the southern hemisphere 2017, and at

11 that time, the committee recommended that the following

12 viruses be used for trivalent influenza vaccines in the

13 2017 southern hemisphere influenza seasons.

14   An A/Michigan/45/2015 H1N1 pdm09-like virus, an

15 A/Hong Kong/4801/2014 H3N2-like virus, and a

16 B/Brisbane/60/2008-like virus which is from B/Victorian

17 lineage. It is also recommended that for quadrivalent

18 influenza vaccines containing two influenza B viruses

19 contain the above three viruses and also a

20 B/Phuket/3073/2013-like virus, which is from the B/Yamagata

21 lineage.

22   So I would like to summarize where we are right

23 now. In a little bit over a week, WHO have the meeting to

24 give recommendations for the influenza virus vaccines

25 compositions for northern hemisphere 2017-2018, and the WHO

1 recommended that the following viruses be used for

2 trivalent influenza vaccines in the 2017-2018 northern

3 hemisphere influenza seasons is an A/Michigan/45/2015 H1N1

4 pdm09-like virus, a change from A/California/7/2009 H1N1

5 pdm09-like virus, but same as 2017 southern hemisphere

6 recommendations.

7   For H3N2, they recommended an A/Hong

8 Kong/4801/2014 H3N2-like virus, and no change from the

9 2016-2017 northern hemisphere recommendations. And a

10 B/Brisbane/60/2008-like virus from B/Victoria lineage, and

11 there is no change from 2016-2017 northern hemisphere

12 recommendations.

13   And they also recommended that a quadrivalent

14 vaccines contain two influenza B viruses, should contain

15 the above three viruses and also a B/Phuket/3073/2013-like

16 virus, which is from B/Yamagata. This recommendation is no

17 change from 2016-2017 recommendations.

18   As in the previous years, the national and the

19 regional control authorities, they are responsible to

20 approve the composition and formulations of vaccines used

21 in each country.

22   So at the end of the discussions for today, the

23 committee will be asked to discuss on which influenza virus

24 strain should be recommended for the antigenic composition

1   of the 2017-2018 influenza virus vaccines in the United

2   States.

3   So I would like to show you the options for the

4   strain compositions for the 2017-2018 trivalent influenza

5   vaccines. For influenza A(H1N1), there are two options,

6   either recommend an A/Michigan/45/2015 H1N1 pdm09-like

7   virus or recommend an alternative H1N1 candidate vaccine

8   virus. For H3N2 influenza A, also have two options, either

9   recommend an A/Hong Kong/4801/2014 H3N2-like virus or

10 recommend an alternative H3N2 candidate vaccine virus.

11   For influenza B in the trivalent influenza

12 vaccines, it has three options. One is recommend a

13 B/Brisbane/60/2008-like virus from B/Victoria lineage, or

14 recommend an alternative candidate vaccine virus from the

15 B/Victoria lineage, or recommend a candidate vaccine virus

16 from the B/Yamagata lineage.

17   So for the options for the quadrivalent influenza

18 vaccines for the second B strain, it also has three

19 options. The first one is recommend inclusion of a

20 B/Phuket/3073/2013-like virus from B/Yamagata lineage or

21 recommend an alternative candidate vaccine virus from the

22 B/Yamagata lineage. The third option is recommend a

23 candidate vaccine virus from the B/Victoria lineage.

24   So before I finish my introductions, I would like

25 to fresh up the slides for the questions the committee will

1 be asked to vote on at the end of the discussions. Those

2 are the two questions for the composition of the trivalent

3 2017-2018 influenza vaccine virus in the United States.

4 Does the committee recommend the following options, and

5 also another question is for quadrivalent 2017-2018

6 influenza vaccines in the United States.

7   This is the end of my presentation. Thank you.

8   DR. MCINNES: Could you please remind me of the

9 vaccines sold in the United States, what proportion of it

10 is trivalent and what proportion of it is quadrivalent?

11   MS. CHEUNG: So basically, right now we have, I

12 would say, it's like eight licensed influenza vaccines, and

13 seven of those they have quadrivalent formulations, but the

14 actual number exactly how many of those are trivalent and

15 how many of those are quadrivalent, I'm not really sure.

16 Jerry, do you have any idea?

17   DR. KATZ: Based on the information that CDC was

18 provided by manufacturers at the start of the season, it's

19 estimated that about 60 percent of the available doses for

20 this past season were quadrivalent, and that has been

21 increasing over the last few years.

22   DR. MONTO: In all the recommendations, the

23 statement of like is included. Who makes the decision

24 about what is like the recommended virus and what is unlike

25 the recommended virus, number one?

1   Number two, how are decisions made about those

2   that are producing cell culture based vaccine and, number

3   three, how is the decision made about sequences used for

4   those who are actually making vaccine in insect cells now?

5   MS. CHEUNG: I think for the like virus questions,

6   I think Jackie will be the best person to respond.

7   DR. KATZ: The WHO collaborating centers perform

8   antigenic analyses. What we refer to as a one-way test

9   where a particular virus is tested using antisera of the

10   reference virus, for example Hong Kong/4801. A two-way

11   test is when that sera from that particular virus is also

12   raised and we look in two ways whether the virus is

13   similar, for example, again to a virus like Hong Kong/4801.

14   So the answer is it's the WHO collaborating centers that

15   determine what's like and what is not like.

16   DR. MONTO: What about the cell culture-based

17   vaccine production?

18   DR. KATZ: Right, so currently two collaborating

19   centers, the CDC and the Melbourne collaborating center in

20   Australia, are producing isolates from the qualified

21   manufacturers cell culture, MDCK cell line, and those

22   viruses are again antigenically tested, compared with the

23   reference vaccine like virus, and then antisera are also

24   raised to those vaccine viruses. I think it was mentioned

 1 earlier that this is similar to the analysis we do for egg-

 2 based vaccines. The third question?

 3   DR. MONTO: How are the sequences determined for -

 4 - because if the question is are these egg-derived

 5 sequences, or are these -- how are the sequences

 6 determined?

 7   DR. WEIR: Actually, the sequence is not a direct

 8 part of the decision. It's our antigenic likeness is based

 9 on hemagglutination inhibition test at this point, not

10 sequencing.

11   MS. CHEUNG: Are you asking about the insect-

12 derived vaccines? I think for the insect-derived vaccines,

13 we are based on the sequence of the working virus.

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

15   DR. WEIR: Cell-based, if we're talking about flu

16 block, that is not based on a sequence. That is a derived

17 reference strain, a candidate vaccine strain that matches

18 antigenically to the like recommended strain. For the

19 recombinant, the manufacturer produces a sequence, and they

20 run it by us in the supplement update and typically -- I

21 mean, it's a fairly limited amount of data, but we have

22 matched it to usually the reference strain of the egg-

23 derived virus, but on the other hand, I have to tell you in

24 the last year we have also considered the wildtype strain

25 too as being acceptable.

1   DR. MONTO: That is what I was wondering.

2   DR. EDWARDS: Karen, would you like to introduce

3   yourself?

4   DR. KOTLOFF: I am Karen Kotloff. I am a

5   pediatric infectious disease specialist at the Center for

6   Vaccine Development, University of Maryland School of

7   Medicine.

8   DR. EDWARDS: Thank you very much.

9   The next presentation on U.S. surveillance will

10   be by Dr. Lisa Grohskopf, who is a Captain in the U.S.

11   Public Health Service and Associate Chief for Policy and

12   liaison at the Epidemiology Prevention Branch in the

13   Influenza Division at the Centers for Disease Control and

14   Prevention.

15   Lisa?

16   **Agenda Item: U.S. Surveillance**

17   DR. GROHSKOPF: Good morning. I am going to

18   present a brief update on U.S. influenza surveillance but

19   also an update on interim vaccine effectiveness estimates

20   for the United States from the U.S. flu VE network.

21   So we'll start with surveillance. The data that

22   are presented in the next series of slides come from CDC's

23   FluView report, which is issued weekly. These data come

24   from the week 8 report, which is for the calendar week

25   number 8, the week ending February 25.

1   The first two slides cover virologic

2   surveillance, and the data for these are basically reports

3   related to influenza positive test results that are

4   reported to CDC weekly from approximately 100 public health

5   laboratories and approximately 300 clinical laboratories

6   via either the national respiratory and enteric virus

7   surveillance system or WHO collaborating laboratories

8   located throughout the United States. This first slide

9   summarizes the data for the clinical labs. By and large,

10 the clinical labs don't subtype flu As. So we are looking

11 at untyped As.

12   We have the calendar week on the X axis, on the

13 left-hand Y axis we have number of positive specimens,

14 which is represented by the lines in the graph, and on the

15 right, by the colored bars and the percent positive

16 specimens on the right Y axis as represented by the lines.

17   Overall, you can see that the flu viruses that

18 predominated were As. We do see an uptick in the Bs in

19 recent weeks of reporting. Just pointing out for the

20 percent positive specimens that we have overall percent

21 positives, the solid black line up top, has leveled off

22 somewhat in recent weeks.

23   If we look at the As, that's the next line down,

24 the dotted yellow one, a bit of a decline in the percent

25 positive for As, but this is somewhat matched by an uptick

1 in the percent positive for Bs as you can see in the bottom

2 line.

3   So this slide summarizes the same data from the

4 same sources, except it's from the public health

5 laboratories. One difference here is that because the

6 public health laboratories typically or often are testing

7 specimens that are already tested in a clinical laboratory,

8 the percent positive parameter doesn't carry as much

9 meaning. So it's not represented here.

10   By and large, public health laboratories do

11 subtype As and determine lineage for Bs. The predominant

12 color for all of these weeks thus far has been red, which

13 is flu A(H3N2). There's relatively little AH N1 pdm09.

14 Those are in orange and probably not terribly visible on

15 the slide. They are there but very small. There was an

16 uptick in Bs in recent weeks, and those are represented in

17 the green at the bottom.

18   This slide summarizes results for genetic testing

19 for flu viruses submitted to CDC. There were total since

20 the beginning of October for the 2016-2017 season of 1,247

21 tested, 154 AH1 pdm09s. I believe 772 H3s, and 321 Bs.

22   For the H1N1 pdm09 of the isolates, the 154 that

23 were tested, 100 percent were the HA gene was genetic group

24 6B.1. For influenza A(H3N2), 96 percent the hemagglutinin

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

2 3C.3a.

3   For the Bs, among the Victoria specimens, 100

4 percent were V1A and among the Yamagata specimens, 100

5 percent were Y3.

6   Next antigenic characterization results. There

7 were a total of 766 viruses antigenically characterized

8 among the H1N1 pdm09s, all 112 were antigenically

9 characterized using ferret post-infection antisera as

10 A/California/7/2009-like, which is the H1N1 component of

11 the 2016-2017 vaccine. Three hundred and eighty-seven of

12 399 or 97 percent of the A(H3N2) isolates were

13 antigenically characterized as A/Hong Kong/4801/2014-like.

14 The H3N2 component of the 2016-2017 vaccine.

15   B/Victoria lineage, 123 of 134, 92 percent

16 antigenically characterized as B/Brisbane/62/2008-like,

17 which is included in both the quadrivalent and trivalent

18 vaccines for 2016-2017, and finally B/Yamagata lineage, all

19 121 that were antigenically characterized were

20 B/Phuket/3073/2013-like, an influenza B virus included in

21 the quadrivalent vaccines for the current season.

22   Moving on to two slides on illness surveillance.

23 This first one is outpatient ILI visits. This comes from

24 the U.S. Influenza Like Illness Surveillance Network, or

25 ILINet. Week of surveillance is on the bottom of the chart

1   on the X axis, percent of visits for ILI are on the Y axis.

2   This network consists of approximately 2,800 outpatient

3   facilities that report each week the percent of outpatient

4   visits that were for an ILI diagnosis, defined as fever of

5   100 degrees or higher and sore throat or -- I'm actually

6   forgetting the last parameter there, I apologize.

7   We have a number of seasons represented on this

8   slide. The 2015-2016 season is represented in red with the

9   triangles. That's the current season. For the most recent

10 week of reporting, the percent was reported as 4.8 percent,

11 which is above the baseline of 2.2 percent still for this

12 season. So still seeing activity in ILI for this season.

13   This is hospitalization data from FluSurv-NET.

14 Hospitalization data is reported overall and by age groups.

15 It's cumulative data. So the lines will continue to go up

16 over the course of the season. Week of surveillance is on

17 the X axis and the rate of hospitalizations per 100,000

18 population is on the Y axis.

19   Overall, considering all age groups as of week 8,

20 the overall incidence of hospitalization for confirmed flu

21 was 39.4 for 100,000 population. The highest

22 hospitalization rate goes for 65 and older for whom it is

23 180 per 100,000 population. That's the highest group for

24 hospitalizations for this season.

1   The last two surveillance slides summarize

2 mortality data. This first one is information on pneumonia

3 and influenza mortality from the National Center for Health

4 Statistics. This information is compiled from death

5 certificate data, and this is current as through February

6 11 and March of -- it's for the week ending February 11 as

7 was finalized on March 2.

8   There is something of a backlog in death

9 certificate data. So these figures do sometimes change

10 during the weeks after they are initially reported, hence

11 the two dates.

12   For the week ending February 11, the overall

13 proportion of deaths reported due to pneumonia or influenza

14 ICD diagnostic codes was 7.8 percent, which is just above

15 the epidemic threshold of 7.5 percent.

16   Last surveillance slide, this is pediatric deaths

17 associated with confirmed flu. This is again several

18 seasons worth of data, starting with 2013-2014 on the far

19 left. For the 2016-2017 season thus far, a total of 40

20 deaths have been reported, including six in the most recent

21 week, week 8.

22   Summary of the U.S. season. Influenza A(H3N2)

23 viruses have predominated during this season. There has

24 been a recent increase in influenza B activity in the

25 recent past few weeks. So far influenza activity has

1 overall been moderate and may have at this point peaked

2 nationally. The circulating strains are similar to those

3 contained in the 2016-2017 vaccine.

4   DR. EDWARDS: Thank you, Lisa. Are there

5 questions? Perhaps I can start. Do you have an idea

6 overall of the overall vaccination rate this particular

7 year?

8   DR. GROHSKOPF: We just recently have gotten a

9 preliminary read on that that was discussed at ACIP. There

10 are data from the National Immunization Survey that -- this

11 is still early and preliminary and the figures do tend to

12 change over time, but we were able to say at ACIP that

13 overall at least for pediatric coverage, which we focused

14 on because it was an issue because of the LAIV discussion,

15 that as of the end of December, the coverage at least in

16 pediatrics was similar to that of the previous season. It

17 was around 50 percent.

18   We anticipate that those figures change over time

19 because data continues to be collected through the season,

20 and that was only through December.

21   DR. MONTO: How did that break down in terms of

22 the lack of availability of live attenuated vaccine?

23 Because there was concern that pediatric vaccinations would

24 drop because of that.

1   DR. GROHSKOPF: Overall, for the pediatric age

2   group, it was 50 percent, I believe, compared with 51

3   percent for the same period of time last year. My memory

4   is that for individual age groups -- and again this was all

5   very preliminary -- there wasn't a difference among the

6   various age groups within the pediatric population compared

7   with the previous season. But I expect we will be hearing

8   more about that as time goes on.

9   DR. MOORE: In your P&I graph, it looks to me that

10   flu rates this season have not been -- or at least flu

11   mortality has not been tremendous this year. We are doing

12   pretty well for that. But if you go back to your ILI

13   slide, where you compare different years for influenza-like

14   illness, it looks like we are actually having a fairly

15   sizeable rate of influenza that may not be caught by the

16   vaccines. So I'm wondering does this mean that we are

17   seeing a high rate of influenza but a low rate of

18   mortality, or should we interpret one graph differently

19   from the other in terms of the surveillance data?

20   DR. GROHSKOPF: That's a really good question. I

21   think it's a little difficult sometimes, oftentimes, to

22   draw parallels between the systems because the sources of

23   data that are used are just so different. The National

24   Center for Health Statistics data does run off basically

25   death certificate reporting, which has its attendant

1   limitations to it, and in this case, what we are getting

2   with the ILInet is data directly from providers basically

3   reporting their proportions of ILI visits as a total

4   function of total outpatient visits. So I think I would

5   hesitate to draw a comparison simply because the data

6   sources are so different.

7   DR. MOORE: What is your opinion on what the flu

8   rates were this year compared to previous years? Are we

9   having an elevated rate of influenza this year, or not?

10   DR. GROHSKOPF: Well, all seasons are different in

11 terms of their severity. They can be different from one

12 season to another in terms of the segment of the population

13 that is most severely affected. In recent seasons we have

14 had some seasons, for example, where hospitalization rates

15 were greater, for example, among 50 through 64-year-olds

16 than we would have anticipated.

17   Things do change, and it's hard to form a stable

18 opinion about the severity of flu. I think just looking at

19 this ILI graph, we had by this account a relatively mild

20 season during 2011-2012. This one, you know, seems at

21 least for ILI activity somewhere comparable between 2014-

22 2015 and 2015-2016, but it's going to be different. It's

23 going to be different each year.

24   DR. MONTO: Just from the view of the CDC-

25 sponsored vaccine effectiveness network, there has enormous

1 variation between sites in terms of occurrence. Seattle

2 has had a rather severe outbreak whereas other parts of the

3 country have not, and I think that will all come out in the

4 wash as the numbers come through. But it has been a very

5 uneven, uneven influenza season this year.

6   DR. BENNINK: Are the majority of the H3s, are

7 they 2A.1s, in the country?

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

9 are.

10   DR. JANES: Are there any data at CDC or elsewhere

11 as far as you aware about morbidity and mortality by types

12 of types, lineages?

13   DR. GROHSKOPF: For the National Center for Health

14 Statistics data, we don't get that for the pediatric

15 mortality data, they do attempt to gather as much clinical

16 information about those cases as possible. I don't recall

17 the overall number for the 40 for this year yet. Among the

18 six that reported during week 8, there were two H3N2s, one

19 H1N1, two unsubtyped and one B. But that's just one

20 microcosm from one week worth of data.

21   They do attempt to get as much information as

22 possible, but it sometimes takes a few months to get --

23 probably the virus type comes earlier, but other clinical

24 information comes much later.

1   DR. EDWARDS: So Lisa, do you want to then go

2 ahead and present the interim VE data?

3   DR. GROHSKOPF: These slides were presented at

4 ACIP roughly two weeks ago and were prepared by Dr. Brendan

5 Flannery and Jessie Chung, whom I am very indebted to for

6 lending them to me.

7   The U.S. flu VE network includes five sites. We

8 have Group Health in Seattle, Baylor Scott and White in

9 Texas, Marshfield Clinic in Wisconsin, University of

10 Michigan in Michigan, and University of Pittsburgh in

11 Pennsylvania.

12   Briefly to summarize the methods, enrollees are

13 outpatients aged at least 6 months or older, with acute

14 respiratory illness or cough, acute respiratory illness

15 symptoms with cough of 7 days or less duration. For this

16 period for this season, the dates of enrollment were

17 November 28, 2016 to February 4, 2017. I'm going to

18 emphasize February 4 is still early, and they are still

19 collecting data. So these figures may change.

20   The design is a test-negative design in which

21 involves comparing vaccination odds among influenza

22 positive RT-PCR positive cases with RT-PCR negative

23 controls. So everybody is ill, but they are classified as

24 cases or controls based on their flu results.

1   Vaccination status is defined as receipt of at

2   least one dose of any 2016-2017 seasonal flu vaccine

3   according to medical records, immunization registries,

4   and/or self-report. VE is calculated as 1 minus the

5   adjusted odds ratio times 100 percent. Things that are

6   adjusted for include study site, age, self-rated general

7   health status, race, and ethnicity, and the interval in

8   days from onset to enrollment, as well as calendar time.

9   For interim results, thus far as of February 4, a

10 total of 3,144 persons were enrolled at five sites. There

11 were 744 or 24 percent that were RT-PCR positive, 76

12 percent were RT-PCR negative. The breakdown by virus type

13 here is in the pie chart: 80 percent were influenza

14 A(H3N2). Influenza A(H1pdm09) and also B/Victoria account

15 only for 1 percent of the total, 7 percent were unsubtyped,

16 and 11 percent were B/Yamagata.

17   This chart summarizes the number of enrolled

18 participants by week with the RT-PCR result and also the

19 percent positivity by week of onset. I just want to draw

20 attention to the percent positivity which is in the -- it

21 is summarized by the line that goes across the graph. This

22 was still having an overall general trend upward as of

23 February 4. So I mention that only because, again, it was

24 February 4 and we may continue to see more positive

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

2 change.

3   So interim adjusted vaccine effectiveness against

4 medically attended influenza for the season as of February

5 4 from this study. For any influenza A or B virus overall

6 across all age groups, adjusted VE was 48 percent with a 95

7 confidence of 37 percent to 57 percent. As we get into the

8 different age groups, once we split into age categories, we

9 of course have a lower number in the denominator and fewer

10 cases. So consequently get some variability and also some

11 widening of confidence intervals.

12   VE ranges for 19 percent in the 18 through 49 age

13 group, to 58 percent in the 50 to 64 percent age group.

14 Statistical significance is there for 6 months through 8

15 years and for 50 through 64 and for 65 and older.

16   For this table, we have the data summarized by

17 virus type. Again, because pdm09 accounted for 1 percent,

18 as did B/Victoria, we are really only able to report

19 A(H3N2) and B, and for B we can't break down by age group,

20 because the numbers are so small.

21   For A(H3N2) overall adjusted VE was 43 percent,

22 confidence interval 29 percent to 54 percent. Again,

23 looking at the individual age groups for H3N2, there is

24 some variability in the point estimates. For influenza B

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

2 percent.

3   In summary, interim results for the 2016-2017

4 season through February 4, 2017, indicate vaccine

5 effectiveness overall of 48 percent against medically

6 attended influenza. This interim estimate is similar to

7 that seen in previous seasons when the vaccine was well

8 matched to circulating influenza viruses.

9   Significant protection against circulating

10 influenza A(H3N2) and B viruses, which were predominantly

11 B/Yamagata, was observed. We're not able to calculate VE

12 against H1N1 pdm09 or B/Victoria, due to the small number

13 of cases. Again, enrollment is continuing. We anticipate

14 that there's a good possibility numbers may look slightly

15 different by the time the season ends and the final data

16 are compiled.

17   Two brief comments. One on VE against influenza

18 A(H3N2). We saw a value of 43 percent here as just

19 mentioned. This is roughly similar to VE against H3N2 in

20 previous seasons with good antigenic match. For example,

21 2011-2012 and 2012-2013 were both at 39 percent. A meta-

22 analysis of test-negative VE studies by Belongia, et al,

23 came up with a figure of 33 percent. The VE against A in

24 this meta-analysis against A(H1N1)pdm09 and B viruses

25 tended to be higher. A(H3N2) viruses have required more

1   frequent vaccine updates, as we know from past seasons.

2   Candidate H3N2 viruses also tend -- have a greater

3   propensity to have antigenic changes after adaptation in

4   eggs.

5   Another thing that's an active area of thought at

6   this point is repeat vaccination. The flu VE network

7   investigators have been going back and looking at prior

8   season vaccination, and it does seem that prior season

9   vaccination is a significant effect modifier in most

10   seasons. The point estimate for the current season, for

11   example, current season only vaccination, will tend to be

12   consistently higher than the current plus prior season.

13   There generally are overlapping confidence intervals, but

14   it does tend to be higher current only as opposed to

15   current plus prior.

16   There is some evidence also for residual

17   protection from the prior season vaccination consistently

18   for B and for H1N1 pdm09, sometimes for H3N2. This is a

19   complex issue that is an actively evolving area of

20   research.

21   This slide I can't read the whole thing,

22   summarizes the flu VE network investigators at the sites

23   and at CDC who I want to acknowledge, and I also want to

24   acknowledge folks in our branch and division who compiled

25   this data and put it together. Thank you.

1   DR. EDWARDS: Thank you, Lisa. Questions? Jack,

2   did you have a question?

3   DR. BENNINK: I'm going to go to the effectiveness

4   or something like that. It's a little bit off the strain

5   selection, but it applies to effectiveness. Last year, I

6   think, in August, your committee put out recommendations

7   not -- did not recommend live attenuated. Is that going to

8   happen again this year, or how are you thinking about that?

9   DR. GROHSKOPF: That is an area of ongoing

10   discussion at ACIP. We did have an update on that topic at

11   ACIP two weeks ago, and I would anticipate there's probably

12   going to be another discussion at ACIP in June, but at this

13   point, I wouldn't be able to predict what the decision

14   would be.

15   DR. BENNINK: On that topic, do you have any

16   advice or things like that for this committee or for the

17   FDA or anything else in terms of that?

18   DR. GROHSKOPF: I can't think of specific advice

19   with regard to strain selection, I don't know if Jackie

20   can.

21   DR. EL SAHLY: Is the receipt of trivalent versus

22   quadrivalent a variable that you look at in terms of

23   vaccine effectiveness? Especially as it pertains to B, I

24   guess.

1   DR. GROHSKOPF: It has not been analyzed at least

2 in the current session that I know of, although the -- and

3 I don't know actually for this season yet what the

4 proportion of quadrivalent versus trivalent received in the

5 population was. They are still compiling that, and again,

6 it's something that may change as the season goes on. But

7 for the 15-16 season, last year, the estimate was that 66

8 percent of the doses given were quadrivalent.

9   DR. EL SAHLY: So the data is collected as to who

10 received what in terms of vaccine effectiveness, comparing

11 the trivalent to the quadrivalent as it pertains to the --

12   DR. GROHSKOPF: They do collect data on the

13 vaccine. It is in general not possible to compare

14 different vaccines for example. It was actually only

15 relatively recently that they were able to start comparing

16 LAIV and inactivated. We have so many different vaccines.

17   DR. KOTLOFF: I have a question about the effect

18 modification from previous season vaccination. So is that

19 seen if it's the same vaccine in the previous year and the

20 current year? And also how have you looked at it the other

21 way around, that if it's the same vaccine, and you have

22 last year's vaccination, but not this year's vaccination?

23 Do you have any sense of what the effectiveness of that is

24 for this year's flu?

1   DR. GROHSKOPF: For this year's I don't know. I

2   think it ends up being something of a difficult thing to

3   study, because some seasons they change, some seasons they

4   don't, and there are three different viruses to compare.

5   By the time they get down to running these types of

6   comparisons, particularly if we have a season like this

7   season, as you probably notice, and I think Dr. Monto

8   alluded to, there are not a lot of cases. The statistical

9   difficulties of doing that kind of analysis get troublesome

10   in terms of lower numbers and much wider confidence

11   intervals that are harder to interpret.

12   I don't know specifically any information that

13   can answer the question you are asking exactly, though.

14   It's something that they are continuing to analyze.

15   DR. EDWARDS: Lisa, I think -- and perhaps the

16   numbers are too small, but it is sort of curious that the

17   age group that you would think would have the most robust

18   immune response, being 18 and 49, actually has the lowest

19   vaccine effectiveness. So is that a matter of numbers or

20   is that a matter of these people are just not as hardy as

21   we were, or what's the story?

22   DR. GROHSKOPF: I wish I had an answer for that.

23   I mean, I do think that at least some of the variability

24   has to do with the numbers, particularly once we sub out by

25   age category, and we have had seasons where for one reason

1   or another efficacy has been greater or less and there have

2   been theories posited about what that particular age group

3   experienced before in terms of exposure to flu or to

4   vaccine. But I don't have an answer.

5   DR. BENNINK: Maybe you answered this, but are

6   there enough numbers that you could tell whether there was

7   a difference, whether the exact previous year they were

8   immunized or not?

9   DR. GROHSKOPF: Oh, you mean for that age group,

10 whether they received vaccine the previous year? I don't

11 know. I think that that information probably exists. I

12 don't know that it has been done, and I don't know the

13 answer to the question.

14   DR. MOORE: So the vaccine efficacy, I am a little

15 worried about the H3, the vaccine strain is not recommended

16 to be changed this year. The vaccine efficacy is not very

17 good, which it generally isn't for H3, but the issue is --

18 and so we can't expect that next year it's going to be any

19 better. At best it's going to be much -- it's going to be

20 the same, and if there is an expansion of a clone that is

21 not fully recognized by the Hong Kong strain, then it is

22 going to be presumably much worse.

23   So now changing the strain recommendation would

24 be at least largely dependent on how well it worked in this

25 part year, and that's the reason why I'm asking the

1   question. Do we have -- do the ILI cases, charts, that you

2   showed indicate that we had a high level of flu activity or

3   should we be looking at the influenza mortality, which

4   suggests that we are having a relatively low level of

5   influenza mortality this past year?

6   So that would suggest that at least we are doing

7   something reasonably well with the Hong Kong strain and we

8   might not want to change it, but if we are actually seeing

9   a lot of influenza occurring this year, then there's a lot

10   more reason for trying to find a better strain selection

11   for the H3 virus.

12   DR. GROHSKOPF: I think one of the difficulties

13   with the mortality other than the pediatric, the all ages

14   mortality, the health statistics, and with the ILInet data

15   is that it's not necessarily confirmed flu. So we are

16   dealing with on the one hand ILI activity which could be

17   other viruses, which will have their own seasonal patterns

18   that may vary from one season to the next and on the other

19   hand, we have death certificate data where we don't know

20   that that was confirmed flu either. It's basically ICD-9

21   diagnostic codes.

22   So, many of which are not completely flu-specific

23   anyway. We don't have test results for those folks, for

24   example. So I think it's difficult to draw very firm

25   inferences from that, for those reasons.

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

2   Our next speaker will be Dr. Jackie Katz. She

3   will present world surveillance and virus characterization.

4   She is the deputy director of the Influenza Division and

5   director of the WHO collaborating center for Surveillance,

6   Epidemiology, and Control of Influenza at the National

7   Center for Immunization and Respiratory Diseases at the

8   Centers for Disease Control and Prevention.

9   Jackie?

10   **Agenda Item: World Surveillance/Virus**

11   **Characterization**

12   DR. KATZ: Thank you. So this morning I am going

13   to present to you pretty much the information that was

14   presented in the WHO information meeting to industry last

15   Thursday in Geneva, and this is a summary of the influenza

16   type A and type B global surveillance and virus

17   characterization that was discussed at the three-day

18   vaccine consultation meeting.

19   So just to remind you, this is the global

20   influenza surveillance and response system, is a WHO

21   network which comprises six WHO collaborating centers, over

22   140 national influenza centers, four essential regulatory

23   laboratories, and a number of H5 reference labs. So we met

24   from February starting on February 27 last week to review

25   all the data.

1   I was the chair of the three-day meeting, and the

2 nine advisors shown here from the WHOCCs and ERLs are the

3 individuals who make the final decision, but all the data

4 is reviewed and discussed by a large body including 24

5 additional observers from various WHO laboratories, as well

6 as the veterinary sector, because we also address zoonotic

7 influenza virus activity and make recommendations for

8 candidate vaccine viruses, but obviously that is not part

9 of my talk today.

10   So I will just start by showing you what the

11 season looked like globally. These are numbers of

12 specimens that were processed each week by different

13 laboratories within GISRS and reported to WHO. So you can

14 see here the tail end of the last season starting here,

15 climbing quite quickly, and this indicates at the end of

16 2016 represents several regions that had quite early

17 activity, and then the rest of the season shown here in red

18 in 2017. So quite a robust season in terms of number of

19 viruses but perhaps not quite as high as our previous

20 season.

21   And I think you have this in your handouts. This

22 again is WHO data, and now breaking down where available

23 the different influenza A subtypes and type B virus

24 information, and if you'll focus on this sort of in between

25 bright bluish teal color, you can see that there was a lot

1   of activity of H3N2 in many regions of the world, followed

2   and virtually very little H1N1 pdm09 activity, except in a

3   few regions, such as late season in Mexico and South

4   America, and again, this is data from September to

5   February. So some of this reflects the end of the southern

6   hemisphere season, but even in the end of the southern

7   hemisphere season in, for example, in Australia, you can

8   see there was quite a lot of H3 activity.

9   Again, this is just showing the epidemiological

10   curve of the global circulation, and again, as Lisa pointed

11   out from the United States it was largely an H3N2 season,

12   with a little of B, and the season has stretched quite

13   long. This is as of week 6.

14   And again, just another representation where you

15   can fully see the viruses reported to WHO through their

16   FluNet system that almost half were H3 viruses, very few

17   H1N1 pdm09s, and a much smaller proportion of influenza B

18   viruses.

19   Shown here is all the different countries that

20   contributed viruses for our antigenic and genetic

21   surveillance from the period of September through February.

22   So you can see we've got a fairly good global

23   representation, but obviously still some gaps in

24   surveillance.

1   So I'll begin with our data on the H1N1 pdm09

2   viruses, and again, these are viruses submitted to the WHO

3   collaborating centers and national influenza centers from

4   September 2016 through February 2017. As we have heard

5   earlier, there wasn't much H1N1 pdm09 activity globally in

6   this period. These maps show the maximum activity during

7   that period in the given countries, and you can see with a

8   few exceptions, like South Africa, India, that had some

9   widespread activity, there's mostly sporadic local activity

10   globally for H1N1 pdm09.

11   So this is a phylogenetic tree of the

12   hemagglutinin gene of H1N1 viruses, and this is all data

13   that was available prior to the consultation meeting last

14   week. That is submitted by the collaborating centers as

15   they perform genetic characterization, as well as some

16   national influenza centers. All the data goes into a

17   global database called GISAID, and this allows the

18   collaborating centers to rapidly pull out and analyze that

19   data.

20   This just shows you by region. It's color coded

21   by region. So each one of these little bars represents an

22   HA sequence. There's a time series, and I know you can't

23   read this, but if you'll just focus on the last several

24   columns here, that is the period September through January,

25   and you can see that there really wasn't a lot of activity,

1   but most of it is the 6B.1 subclade or clade of viruses,

2   and I'll just remind you, so for the last couple of

3   seasons, we have had two H1N1 pdm09 subclades circulating,

4   the 6B.1 and the 6B.2. So in this period, very little

5   6B.2, and what was out there was 6B.1.

6   The other thing I just want to highlight is that

7   this tree in general is pretty straight. It's not moving

8   to the right, which would suggest that the viruses are

9   changing genetically, and so this is also demonstrated

10   here. If you are following along on your handouts, I've

11   switched up the order just slightly for some of this

12   genetic analysis, but this is just again to emphasize that

13   in most regions of the world, there was predominating 6B.1

14   subclade of H1N1 viruses, with very little 6B.2, a couple

15   of viruses in Oceania and in Asia, and Africa still has a

16   little bit of the oldest 6B viruses, and we typically see

17   that the African continent is somewhat behind in terms of

18   viruses, but everybody else throughout the world has pretty

19   much switched to 6B.1.

20   And if we take a look at in a little more detail

21   at a condensed phylogenetic tree of the hemagglutinin gene,

22   you can see the breakout within the 6B clade of the 6B.1

23   and the 6B.2 viruses, and again, there's not a lot of

24   genetic diversity happening in the 6B.1 viruses right now.

25   Just to orient you with what you're looking at here, these

1 are names of viruses. The color codes indicate the months.

2 So the orange and pink are the most recent viruses from

3 December and January, the blue and green are slightly

4 older, October, November viruses.

5   Also the virus that was still the vaccine virus

6 in the 2016-2017 vaccine for the northern hemisphere, as

7 you know, was the California/7 shown here, and then the

8 Michigan/45/2015 virus which is a 6B.1 virus, was

9 recommended for the 2017 southern hemisphere vaccine, and

10 that was considered a slight update to represent the

11 viruses, the genetic viruses, that were circulating as well

12 as some data that we obtained with antigenic differences as

13 we could see through human serum, and I'll focus on that

14 again in a moment.

15   So the only changes we are seeing is there's a

16 small cluster here. These are mostly U.S. viruses, and

17 they have three key substitutions at 205, 183, and 166, but

18 many of our colleagues around the world are not seeing

19 these viruses yet, and they still just represent a small

20 proportion.

21   If we look at the neuraminidase gene, again the

22 phylogenetic breakdown, the viruses fall into the 6B.1 and

23 6B.2 groups, and again there isn't a whole lot of genetic

24 diversity that we are seeing there.

1   But if we consider the California/7/2009 vaccine

2   virus and compare it with the more recent 6B.1 reference

3   virus, Michigan/45/2015, we can see -- and this is a three-

4   dimensional structure of a monomer of HA. Shown here are

5   the different antigenic sites in the head of the molecule,

6   and shown over to the right, the red areas indicate where

7   amino acid changes have occurred in the 6B.1 viruses, and

8   so we know that these viruses have accumulated

9   substitutions in both antigenic site SB and in antigenic

10 site SA, which the more recent change at 162, which affects

11 glycosylation for the 6B.1 viruses. And there's also

12 changes in site CA for the H1N1 viruses.

13   This is a slide I showed you back in October, and

14 it's a way to remind you of the additional analysis we did

15 for H1N1 viruses back for the September meeting, and which

16 contributed to our change in the vaccine virus

17 recommendation and the move to Michigan/45. So what we had

18 done in that analysis last year was to take our panels of

19 pre- and post-vaccination adult human sera from individuals

20 that received the vaccines through from 2010 to 2016 and

21 all of these vaccines included the California/7/2009

22 component.

23   So all of these individuals were vaccinated with

24 California/7, and we looked specifically at adults because

25 of some literature that Scott Hensley and others had

1 developed in terms of finding a certain middle age group

2 that they felt weren't responding to the California/7 virus

3 as vaccine virus and making antibody responses to more

4 contemporary viruses.

5   So we looked at adults and characterized their

6 potential priming history based on the year that they were

7 born, and based on their profile of their pre- and post-

8 vaccination response to historic former seasonal H1N1

9 viruses, and we could determine three different profiles.

10 We could determine individuals that were likely primed with

11 USSR/77-like viruses, and they had two different

12 phenotypes. One group shown down here, when they were

13 vaccinated with California/7 made robust responses to the

14 vaccine virus, and then to all other viruses, including

15 different 6B.1 viruses.

16   But there was a subset of the population that,

17 although they responded to California/7, they failed to

18 make antibody that cross-reacted with the more contemporary

19 6B.1 viruses, including the Michigan/45/2015 virus shown

20 here.

21   So last, for the September vaccine consultation

22 meeting, we and a couple of other groups used pooled sera

23 from individuals with this phenotype as well as this

24 phenotype and were able to discriminate by the HI assay

25 some differences with the currently circulating viruses,

1   and that's shown here in this H hemagglutination inhibition

2   assay, and just to remind you how we set these assays up

3   and what this is telling us, we have a number of reference

4   viruses including the California/7/2009 viruses propagated

5   in eggs or cells, and these represent the vaccine virus,

6   and then other contemporary circulating viruses.

7   Across the top here we have reference ferret

8   antisera raised to these reference viruses, and the top

9   panel tells us how well this antisera reacts with its

10 homologous virus, which is highlighted here in red. Then

11 we have a series of test viruses from circulating viruses

12 we have just isolated, and we look at how well these

13 viruses are covered by the ferret antisera in the HI test.

14   Shown in yellow are the antisera raised to egg or

15 cell propagated California/7/2009, and you can see that the

16 titers that we get with the circulating viruses are very

17 similar to the homologous viruses, suggesting that these

18 viruses are all similar to the California/7 vaccine

19 reference viruses.

20   Similarly, if we use ferret antisera raised to

21 our reference 6B.1 virus, Michigan/45/2015, you can see the

22 same thing, that we have high homologous to the egg and the

23 cell propagated viruses, and these antisera react well

24 mostly within twofold, occasionally within fourfold, of

1 that homologous titer, again suggesting that the viruses

2 are well covered by sera to Michigan/45.

3   If we look over here now in the pink, we have

4 highlighted the post-vaccination human serum pool that we

5 are using, and so these are individuals that have received

6 the trivalent or quadrivalent vaccines over the years, and

7 they make robust responses to the California/7 vaccine

8 component, but when we look at their responses to 6B.1

9 circulating viruses, we can see most of these are at least

10 eightfold or greater reduced, suggesting that at least in

11 the subset of adult human sera, we can discriminate that

12 there is an antigenic difference with more contemporary

13 6B.1 viruses, compared with the California/7 vaccine virus.

14   And if we look at this by antigenic cartography,

15 and this is done by our colleagues at Cambridge University,

16 here they have both the California/7 vaccine virus

17 represented in blue, the Michigan/45 represented in red,

18 and because this data is derived from our HIs with ferret

19 antisera, we are not seeing any difference. The 2016-2017

20 viruses are all clustering very tightly around either one

21 of these viruses, just as earlier viruses also did.

22   So in summary, this was the tables that we always

23 put together for the different collaborating centers, and

24 their analysis. So here I have both the similarity with

25 the California/7/2009 vaccine, as well as the

1 Michigan/45/2015 vaccine component which is recommended for

2 the 2017 southern hemisphere, and you can see that we are

3 getting very good antigenic similarity, indicating that

4 these viruses have not moved on and that Michigan/45/2015

5 antisera covers all of the viruses that we analyzed very

6 well.

7   We also look at in a different analysis, we use

8 human serology, using contemporary panels of pre- and post-

9 vaccine sera. So these are panels of sera, and there were

10 two sets of different panels, and the different

11 laboratories use different panels. So for the data I'm

12 about to show you, this was data from CDC and other groups

13 that used a U.S. panel of pediatric, adult, and elderly

14 sera, sera from Japan from adults and elderly, and from a

15 UK adult population, and you can see that all of these

16 vaccines contained the California 07/2009 component.

17   So if we look at -- we're color coding here now

18 by the different panels -- this is just the adult sera, and

19 we're comparing the responses to the cell-propagated

20 California 07/2009, which is shown over here. So we're

21 setting that response at 100 percent, and then we're asking

22 for each of the other more contemporary circulating viruses

23 representing either the 6B.2 subclade or 6B.1 viruses how

24 well the antibody that is raised to California/7 covering

25 these different viruses.

1   And you can see with the exception of the U.S.

2   panel that most of the viruses are covered quite well. One

3   exception is a 6B.1 Montana 2016, and that virus represents

4   that small genetic group that we're seeing in U.S. at the

5   moment, but not seeing anywhere else, and it's really not

6   the predominating virus, but we used it as a vaccine

7   antigen or a circulating virus antigen in this study.

8   Using the U.S. sera, and we had very robust

9   responses in our U.S. panel such that we had a very big

10   window to discriminate the different reactivities, if we

11   look at the U.S. sera we are seeing reductions to the 6B.2

12   and the 6B.1 Michigan/45 cell-propagated and then Indiana

13   21/2016 cell-propagated 6B.2 virus, but that wasn't as

14   evident in the other panels of sera that we looked at.

15   So in summary for the H1N1s, activity was

16   generally quite low globally in the period September 2016

17   through February 2017. And the vast majority of viruses

18   were 6B.1 and the 6B.2 subclade was really detected at only

19   a very low level.

20   The majority of recent viruses were antigenically

21   indistinguishable from the current California/07/2009 and

22   Michigan/45/2015 vaccine virus components if we used ferret

23   antisera in the HI tests. However, we saw the same

24   phenomenon we saw back in September where if we used a

25   panel of human serum from adults that likely were in that

1   middle-age group that had experienced USSR 77 as their

2   priming H1N1 virus, then we could discriminate antigenic

3   differences with the contemporary circulating 6B.1 viruses.

4   And if we looked at post-vaccination geometric

5   mean HI titers, we saw in some adult and pediatric sera

6   tested that there were reductions to some of the

7   contemporary 6B.1 and 6B.2 viruses, but this wasn't

8   universally seen, and it was overall less pronounced in

9   most of the panels we looked at.

10   So moving on to the H3N2 viruses. As we've

11 already heard, there's a lot of activity in the period

12 September 2016 to February 2017. Widespread activity in

13 North America and parts of Europe and Asia and even

14 regional outbreak activity at the end of the southern

15 hemisphere season in Oceania.

16   Again, we're looking at a phylogenetic tree of

17 the hemagglutinin genes. These represent all of the

18 viruses that we had available to us, all the sequences we

19 had available to us, prior to the consultation meeting, and

20 you can see that, again, each colored bar represents a

21 sequence from a virus in a particular region, and now I

22 want to point out that this tree as we often see for the

23 H3s, is moving to the right, and you see that there's a lot

24 of genetic subgroups, a lot of little clusters forming

25 here.

1   The predominance of viruses were 3C.2a viruses

2   globally, and we also saw what we're now referring to as

3   the 3C.2a1 subclade, and these were actually, as you can

4   see, from the period September through January, quite

5   predominant, although there were still some 3C.2a activity,

6   but much less 3C.3a activity.

7   And just to look at this in a slightly easier

8   way, you can see this is the different regions by month of

9   detection. And you can see the breakdown here, the 3C.2a

10   in the dark orange, the 3C.2a1 in the light orange, so if

11   you look at the pie charts down the bottom, you can see

12   that that paler orange 3C.2a1 is really in many regions

13   overtaking the 3C.2a's.

14   So in Europe and North America, and most of this

15   is U.S. data, you can see about two-thirds of the viruses

16   were 3C.2a1 and a little over a quarter or so of the

17   viruses or one third of the viruses were 3C.2a. At the

18   tail end of the southern hemisphere season in Oceania, they

19   had a late 3C.3a burst as we did in the prior northern

20   hemisphere season, and in Asia and Africa, there's still

21   more 3C.2a viruses. So particularly in Asia it's still

22   about 50/50 3C.2a compared with 3C.2a1.

23   So if we look in a little more detail at the

24   hemagglutinin gene and what we're seeing. So the 3C.2a1

25   viruses are a subset of 3C.2a's, and they are characterized

1 by having mutations in the HA at amino acids 171, 406, and

2 484, the latter two being in the HA2 region of the

3 molecule. And you can see that there are several subgroups

4 forming. In addition, many of these viruses now have

5 acquired a change of 121 K, and this upper cluster now is

6 the group that is actively forming different genetic

7 subgroups. In particular we're seeing additional changes

8 at 140 and one change at 135 K which involves a potential

9 loss of a glycosylation site.

10   And you can see that a couple different places

11 here. So these are the ones we're keeping our eye on, and

12 I'll focus on the change at 121 K with the 135 K

13 substitution in some of the antigenic analysis.

14   If we look down at the 3C.2a's and of course our

15 Hong Kong/4801 vaccine virus is down here at the base of

16 the 3C.2a viruses, you can see that again there's two major

17 subgroups forming, shown in this phylogenetic analysis.

18 There's a group that has substitutions at 121 K and 144 K,

19 and another group that has substitutions at 131 K and 142.

20 So it's a very dynamic and diverse genetic landscape of

21 H3N2 viruses at the moment. There still was some 3C.3a

22 activity, but as you saw from that pie chart, we really

23 didn't see the burst of 3C.3a activity that we were

24 concerned about at the end of last season. It was truly a

25 3C.2a and a 3C.2a1 season in the United States.

1   Again, there's a little bit of genetic diversity

2   going on in the neuraminidase gene, but essentially the

3   viruses fall out into these same clades and subclades that

4   I've already described.

5   And this is really complicated but how we're

6   trying to look at this is by month, from September through

7   January, what is the frequency of these different genetic

8   groups. And I'm just going to focus on a couple of things

9   here. For the 3C.2a viruses, you'll remember I just called

10 out the group that had changes at 131 and 142 shown in the

11 orange, and the group that had changes at 121 and 144 shown

12 in the purple.

13   So you can see from September that these two

14 lineages have really -- these two clusters of genetic

15 groups have really taken over the 3C.2a's. The 3C.2a1's

16 are much more heterogeneous. We've got many different

17 groups and I just highlighted the three groups that we're

18 really keeping our eye on in the previous tree, and the

19 only thing I'll point out here -- because this does remain

20 pretty heterogeneous -- is perhaps a slight increase in the

21 pale green here, this proportion of viruses that have

22 changes at 121 and that 135 K change that's increased over

23 the period we've been looking at.

24   So before we talk about antigenic

25 characterization of H3N2 viruses, I need to remind you that

1 this is difficult still because the viruses, the 3C.2a

2 viruses that are cell-propagated, many of them have low or

3 undetectable hemagglutination activity with red blood cells

4 in the presence of oseltamivir, and we have to use

5 oseltamivir in our HI assays now to control for changes in

6 the neuraminidase upon cell culture that can confer some

7 binding of the neuraminidase to the red blood cells. So we

8 want to remove any possibility of looking at neuraminidase

9 involvement, and that's why we add oseltamivir.

10   So only about 50 percent or less of viruses can

11 be characterized by the HI assays. At CDC, we're at the

12 higher end of this, we can now test about 50 percent of our

13 viruses by HI, and that's up from about 25 to 30 percent in

14 the previous year. But in addition, all of the WHO

15 collaborating centers are doing one or other sort of virus

16 neutralization assay, typically what we call either a

17 plaque or focus-reduction assay, or a micro-neutralization

18 assay. And these data are supplementing the data that we

19 can obtain by HI.

20   So again this is an HI tree, an HI table. If

21 you'll focus just on the numbers highlighted in yellow,

22 again, these are antisera now raised to reference viruses

23 grown in cell culture that are Hong Kong/4801-like. In

24 many cases, and this is an example of CDC data, we can't

25 actually use the Hong Kong/4801 virus itself. It doesn't

1 have sufficient HA activity in HI assays. But we can use

2 these two reference viruses, Michigan/15 is our reference

3 virus, and you can see here if we use the homologous titer

4 of this virus, we can see that the circulating test viruses

5 are all well inhibited by either this antisera or another

6 antisera raised to another Hong Kong/4801-like virus, Hong

7 Kong/7127.

8   If we look at the egg-propagated Hong Kong/4801

9 virus and antisera raised to it, you can see in this table

10 we generally have the viruses, circulating viruses, are

11 still well inhibited, they're having titers that are within

12 fourfold of this homologous titer of 1280, but there are

13 more examples where we see bigger differences, and you'll

14 see even more of this in the neutralization tables.

15   We also have antisera raised to two 3C.2a1

16 viruses. One is a cell-propagated virus, Amman, and you

17 can see again that antisera raised to this virus covers the

18 circulating viruses quite well. However, an antisera

19 raised to an egg-propagated 3C.2a virus, Alaska/232,

20 doesn't cover the circulating viruses nearly as well, and

21 in fact covers the viruses less well than the Hong

22 Kong/4801 antisera raised to the egg-propagated virus.

23   We also have over here, I should have mentioned

24 earlier, we're breaking these viruses down by their genetic

25 clade, or subclade, and over on the far right we have key

1   substitutions that I've mentioned earlier. So we're really

2   tracking the antigenic profiles of all of these genetic

3   subgroups that are popping up. And the bottom line, by HI,

4   you'll see some viruses here in the 2a's, the two different

5   groups I mentioned, and in the 3C.2a1's, the different

6   genetic groups I've mentioned there, and you can see that

7   these viruses are well covered by antisera raised to the

8   Hong Kong/4801-like viruses.

9   This is a neutralization test, a plaque-reduction

10 assay, showing similar data. This is from our colleagues

11 at the London collaborating center, and here, too, they

12 have to use a surrogate Hong Kong/4801-like virus

13 propagated in cells. That's shown in the highlighted red

14 here. It's the Hong Kong/7295/2014 virus, and you can see

15 antisera raised to this virus recognizes well the majority

16 of circulating viruses tested. Again, these are viruses

17 that were selected for the test because they have the

18 different genetic changes that we're monitoring.

19   Antisera to the Hong Kong/4801 egg-propagated

20 virus covers the viruses less well, as we saw in HI. And

21 in neutralization tests this is more exacerbated in some

22 labs more than others, because of the particular properties

23 of the ferret antisera.

24   This is just the final antigenic test for H3N2.

25 This is a focus reduction neutralization test from the CDC,

1   and you can see again that sera raised to either the cell-

2   propagated Michigan/15 or Hong Kong/4801 that we can use in

3   this test, in neutralization tests, covers the circulating

4   viruses very well. And again, it's the different virus

5   3C.2a1 and 3C.2a viruses tested, represent the gamut of

6   different genetic changes that we're seeing.

7   So, overall, we're not seeing a lot of antigenic

8   change between 3C.2a and the 3C.2a1 viruses, and that's

9   highlighted in the antigenic cartography. The 2a's are in

10 the brighter red, I'm not sure how well you can see it, the

11 3C.2a1's are in the darker red, and we're seeing that

12 they're clustering. The Hong Kong/4801 egg virus is on the

13 edge of that cluster, and you can see now that the cluster

14 is becoming more distinguishable from the earlier 3C.3a

15 viruses represented by Switzerland, which was our former

16 vaccine candidate in previous years.

17   But you can see that there's really overlap

18 between the 3C.2a and the 2a1 viruses. And this is HI

19 data. And the same is true of the neutralization data,

20 it's just the data is a little more spread out because of

21 there's just a little more heterogeneity in the titers of

22 different neutralization assays.

23   So if we look at antisera raised to cell-

24 propagated -- and now we're looking at how well all of the

25 circulating viruses tested by all of the different

1 laboratories -- how well antisera to a Hong Kong/4801-like

2 virus cover these, we can see that overall we get about 93

3 percent of the viruses can be characterized as Hong

4 Kong/4801-like, with a smaller proportion, 7 percent, that

5 are, we would say, show a greater reduction of eightfold or

6 greater, and we would characterize as antigenically

7 distinguishable.

8   If we use the antisera raised to the egg-

9 propagated Hong Kong/4801, we don't get as good coverage,

10 as I mentioned earlier, and it's around 60 percent now

11 cover the viruses and 40 percent are not covered by this

12 antisera. And if we look at data by the virus

13 neutralization assays, we see that these numbers fall a

14 little, but overall, again, the viruses tested by the

15 different labs, most are well covered by the antisera

16 raised to Hong Kong/4801, and we actually see, because of

17 the problems with using Hong Kong/4801 egg-propagated virus

18 and its antisera, in many of the virus neutralization

19 assays, we get extremely high homologous titers, and even

20 though the titers to the circulating viruses which are all

21 propagated in cells, they still have robust titers. It

22 just is, compared with that very high bar of a homologous

23 titer, they all fall or predominantly fall into the low,

24 that they're not being well covered by that antisera.

1   If we look now at -- this is an example again of

2   the three panels of pre- and post-vaccination adult sera,

3   this is again CDC data using the microneutralization test -

4   - and here we're comparing, this is the vaccine virus, Hong

5   Kong/4801, we're comparing the response to that cell-

6   propagated virus. It's set here at 100 percent.

7   The numbers above here are the actual geometric

8   mean titers of the different panels that we looked at. And

9   you can see -- it's probably hard to see -- but we have a

10   dotted line here set at 50 percent, and we're considering

11   reductions if we're seeing significant drops below that red

12   dotted line. And you can see for all the cell-propagated

13   3C.2a1 viruses that were tested, a number of them here, and

14   an additional contemporary 3C.2a virus, that all of these

15   viruses, the antibodies raised to Hong Kong/4801 vaccine

16   virus, are reacting very well, similarly if not better than

17   to the vaccine virus reference virus itself.

18   If we look at egg-propagated viruses, and this is

19   one of the problems we have with egg-propagated viruses, we

20   get extremely high titers, and this is also reflected in

21   our human serology data. But overall, these egg-propagated

22   viruses, if we compared them with egg-propagated Hong

23   Kong/4801, we would also not see any drops in titer. So

24   overall, we're seeing that the circulating 3C.2a1 and 2a

25   viruses are -- that antibody raised to the vaccine virus

 1   Hong Kong/4801 is still reacting well in human sera against

 2   these more contemporary circulating viruses.

 3   And this is just another example of that. These

 4   are two additional human serum panels that some of the labs

 5   used. A China, we had pediatric, adult, and elderly, and

 6   Australian adult and elderly, and what's relevant here

 7   again is that they contained the Hong Kong/4801-like

 8   vaccine virus, and so this is data from Australia looking

 9   at adults vaccinated with the 16/17 QIV or TIV, or their

10   Australian season, past season, 2016 vaccine. And again if

11   you look at the dotted line of 50 percent response, and we

12   look at the response -- this is HI data now, and they've

13   used the Michigan/15 as their Hong Kong/4801-like virus --

14   you can see that's set at 100 percent, and a contemporary

15   3C.2a and a 3C.3a virus, are all very well covered by the

16   antibodies that is raised against the Hong Kong/4801

17   vaccine component.

18   So in summary for H3N2, we did see a high level

19   of activity in many regions of the world, and the majority

20   of viruses fell into phylogenetic clades 3C.2a and subclade

21   3C.2a1. Ferret antisera raised against the cell-propagated

22   3C.2a viruses, for example the Hong Kong/4801-like viruses,

23   well inhibited a majority of viruses tested, either in the

24   HI or the virus neutralization assays.

1   And these included viruses within both the clade

2 2a and the subclade 3C.2a1, and also included a lot of

3 those different little clusters that have formed and

4 included are fairly diverse, genetically diverse, groups of

5 viruses.

6   We saw less well coverage with antisera raised to

7 the egg-propagated viruses, and as you know, egg

8 propagation introduces additional changes that may affect

9 antigenicity. And it's particularly problematic for recent

10 H3N2 viruses. And overall the sera obtained from post-

11 influenza vaccination human serology panels recognized the

12 more contemporary 3C.2a and 3C.2a1 viruses well, regardless

13 of the serologic test we used.

14   I'll move on to influenza B viruses. Again, not

15 too much activity, some local activity in different parts

16 of the world, in central South America, with some sporadic

17 regional or widespread activity in just a few locations in

18 Africa.

19   This is data from the WHO. They collected

20 information, a total of over 15,000 B viruses, but a much

21 smaller proportion, only about a little more than 20

22 percent, was actually had the lineage determined. But

23 where the lineage was determined there was slightly more

24 B/Victoria viruses at 58 percent, compared with B/Yamagata

25 at 42 percent, so that's the overall global picture.

1   If we look and break it down by month now, and

2 these again are these pie charts. The orange reflects the

3 B/Victoria, the clade V1A. The blue, dark blue, reflects

4 the B/Yamagata lineage, the Y3 clade that is circulating.

5 And you can see by region that there was both circulating,

6 that it really depended on the region as to which lineage

7 predominated. In North America, as Lisa Grohskopf

8 mentioned earlier, there's been a later uptick in

9 influenza/B, and at the present time the B/Yamagata is

10 slightly pushing out the B/Vics, but overall in North

11 America it's close to 50/50 as it is in Europe. The

12 Oceania, at the end of the southern hemisphere season, had

13 a surge of the Yamagata, whereas in other regions like

14 central South America, Asia, and Africa, they're still

15 almost three-quarters predominating B/Victoria. So a very

16 diverse picture.

17   And down below you can see this is all the data

18 tracking over time and you can see it just changes month by

19 month, and there's just this constant cycle of one lineage

20 being a little ahead of the other.

21   Focusing first on the B/Victoria lineage viruses,

22 again this is all of the data that was available to us.

23 Each little line represents a sequence coming from a virus

24 in the color-coded regions. The activity that we did have

25 from September to January is all the V1A lineage, and

1 again, not too much diversity happening in the B/Victoria

2 hemagglutinin gene. All of the V1A viruses have changes at

3 129 and 117, and apart from that, there's just a few

4 sporadic things.

5   One thing that we did see in the United States,

6 and we've only seen -- so the viruses that we've seen since

7 September are, we've only seen a few of these viruses in

8 the United States -- and there's a small cluster here that

9 have a deletion of two amino acids at the tip of the

10 molecule. And this is in an antigenic site, and this does

11 have an antigenic impact, as I'll mention in a moment. But

12 the other collaborating centers are searching for these

13 viruses, they haven't seen them yet.

14   Again in the neuraminidase gene, not a lot going

15 on there, or V1A. These are older viruses, but just to

16 remind you that we occasionally see reassortants between

17 the lineages, and these are some older viruses from 2016 or

18 so, that have the Yamagata hemagglutinin and B/Victoria

19 neuraminidase.

20   So if we look at an HI table for the B/Victoria

21 viruses, again highlighted in yellow is the Brisbane/60

22 virus, either grown in eggs or grown in cells. Across the

23 top are the antisera that we've used, and we're comparing

24 the circulating test viruses, and these are viruses, a lot

25 of them from the United States, but some from Europe, Asia,

1 and Africa, and they're all the V1A clade, and you can see

2 that the majority of these viruses are antigenically well

3 matched with antisera to the either egg-propagated or cell-

4 propagated Brisbane/60. We do see some more fourfold

5 reductions with antisera raised to the egg-propagated, but

6 they're still considered Brisbane egg-like.

7   The exception are these viruses highlighted in

8 blue, and these are the ones that have the deletion. You

9 can see that this small group of viruses is antigenically

10 distinguishable from the B/Brisbane, but as I said these

11 are a small handful of viruses that we're seeing in the

12 United States, and at this time what we're doing now is

13 we're preparing antisera to these viruses to see if looking

14 with that antisera whether we'll see antigenic differences

15 or not, but we don't have that data available yet. These

16 are very recent viruses.

17   And this is just to also demonstrate that the

18 Texas/2/2013 antisera raised to cell-propagated Texas/2

19 virus also covers those circulating viruses very well, but

20 again the viruses that have this deletion are not well

21 covered by this antisera, indicating that they're likely

22 antigenically distinguishable from either Brisbane or Texas

23 viruses.

24   If we look at the antigenic cartography, it's

25 telling us a story similar to what we saw previously. The

1 B/Brisbane/60 vaccine virus is shown here in red, this is

2 the cell-propagated, and you can see that the 2016-2017

3 viruses shown in yellow are clustering tightly around it.

4 The egg-propagated is a little more distant and that's

5 because some groups, their antisera raised to egg-

6 propagated Brisbane is a little more variable and doesn't

7 cover these viruses as well.

8   The U.S. data -- so this is a summary of that

9 data now, for all of the collaborating centers -- and you

10 can see with our CDC data, we still get very good coverage

11 with our antisera raised to egg-propagated Brisbane,

12 similar to what we see with cell-propagated. Whereas some

13 of the other collaborating centers have antisera that

14 doesn't recognize circulating viruses as well if they've

15 got the sera raised to egg-propagated. But everyone is

16 seeing a high level of similarity if we're comparing with

17 antisera raised to cell-propagated Brisbane.

18   This is again the true measure of whether we're

19 seeing antigenic similarity or difference. And the

20 differences we see here with egg are changes that we know

21 occur with egg adaptation.

22   If we look at panels of human sera, and these are

23 similar panels that I've already described so I won't go

24 over them again, but this is now a compilation data from

25 multiple laboratories that tested -- what we're comparing

1 here is the cell-propagated B/Brisbane reference virus and

2 the antibody response elicited by the 2016-2017 vaccine

3 containing the B/Brisbane component, and you can see with a

4 few exceptions that these viruses are well covered.

5   This is a deletion mutant, so this is a sort of a

6 rare virus, as is the Yokohama, and these are not covered

7 as well. If we look at all viruses, some of them are not

8 as well covered. But this example is again well covered.

9   We move on to B/Yamagata. So again, virtually

10 all of the viruses detected in this period were of the Y3

11 lineage, and you can see some activity here in the recent

12 months. If we look at a smaller tree we can see that

13 viruses in pink and orange from recent months are all

14 falling in the Y3 clade, and there's again not a lot of

15 genetic diversity. There's some changes that are going on

16 at residue 212 in a small group of viruses, or residue 252

17 in another small group.

18   Again, here we are seeing occasionally some

19 reassortant viruses. And just to remind you, the reference

20 virus, the vaccine virus here is the B/Phuket/3073/2013

21 virus.

22   Again, this is the neuraminidase. The vaccine

23 virus is squarely in the center of the tree. There are

24 some genetic changes here, but not ones that we're really

1 tracking to make changes for strain selection. And there's

2 the rare Y2 virus there.

3   So if we look at the hemagglutination inhibition

4 assay, this is a representative of data obtained from CDC,

5 and shown in the highlighted yellow are the antisera raised

6 to the B/Phuket/3073 vaccine virus, either egg-propagated

7 or cell-propagated, and you can see again that the

8 circulating test viruses from the United States and central

9 South America, and one virus here from Oceania, are all

10 well covered by the Phuket/3073 antisera, suggesting that

11 these viruses are Y3 viruses, are still antigenically

12 similar to the vaccine virus.

13   We also see that here, when we break down all the

14 data from all the different collaborating centers, again,

15 if we compare with antisera raised to egg-propagated

16 Phuket, over 93 percent of the viruses are antigenically

17 similar, 7 percent are low. And we see the same result if

18 we look at antisera raised to cell-propagated Phuket.

19 Again, overall, 93 percent of the viruses tested are

20 characterized as being Phuket-like.

21   And again just showing this in a different way,

22 here's an antigenic cartography visual, using HI data. You

23 can see the B/Phuket/3073 egg-propagated vaccine virus

24 shown in red, and the cluster of 2016 and 2017 viruses

25 circulating. Some of these viruses that are a little more

1 distant reflect some of the greater differences that were

2 seen in a minority of viruses for some collaborating

3 centers.

4   If we again look at human post-vaccination sera

5 from individuals that received the 2016-2017 northern

6 hemisphere vaccine, this is again compared with the

7 reference virus cell-propagated Phuket, set here at a 100

8 percent, you can see that the different circulating viruses

9 tested were all well -- the antibody raised to B/Phuket

10 covered well and reacted well with these different

11 circulating viruses. So the B/Phuket vaccine virus is

12 still reacting very well with circulating B/Yamagata

13 viruses.

14   So summarizing, the influenza B viruses,

15 B/Victoria, B/Yamagata lineage viruses, co-circulated at

16 similar levels in some regions while in other regions the

17 B/Victoria predominated in many countries.

18   B/Victoria lineage viruses all belong to clade

19 1A, it's the same clade we've seen for a number of seasons

20 now, and recently circulating viruses are well inhibited by

21 either ferret antisera raised to the cell culture-

22 propagated Brisbane/60/2008 or the Texas/2/2013.

23   When we looked at human post-vaccination sera, we

24 saw that there were some reductions compared to Brisbane,

25 but this wasn't universally seen. The B/Yamagata lineage

1 viruses -- almost all of the viruses belong to clade 3, and

2 the recently circulating viruses were well inhibited by

3 antisera raised to either cell- or egg-propagated Phuket.

4 And for the human post-vaccination data, again, the

5 B/Phuket vaccine virus raised antibody that reacted well

6 with circulating B/Yamagata lineage viruses.

7   So that brings me to the recommendation, which

8 you've already seen earlier, but last week on Thursday WHO

9 announced that recommendations for the 2017-2018 northern

10 hemisphere influenza vaccine composition, and that was an

11 A/Michigan/45/2015 (H1N1)pdm09-like virus, a Hong

12 Kong/4801/2014 (H3N2)-like virus, and for the trivalent

13 vaccine, a Brisbane/60/2008-like virus. For the

14 quadrivalent vaccine, the second B component was

15 recommended to be the B/Phuket/3073/2013-like virus.

16   And just before I finish, I just wanted to

17 mention some of the new features that we're introducing in

18 our vaccine virus selection. Clearly, as I presented last

19 season, or the October VRBPAC meeting, we're recognizing

20 that additional human serologic studies, particularly

21 evaluating different birth cohorts, can make a difference,

22 and so we're working to have better panels that we can do

23 this for, perhaps also to address some of the questions for

24 H3N2 VE where we're seeing some age-associated effects.

1   The other thing that we're doing now for each

2 vaccination consultation meeting is we're hearing a report

3 from the global influenza vaccine effectiveness group. So

4 last week Alicia Fry from the CDC presented the data on

5 behalf of the GIVE Consortium, and we heard the interim

6 2016-2017 results for H3N2 and B, and Lisa Grohskopf just

7 told you about the U.S. data, but there was similar data

8 from other regions, Canada. We also had the final

9 estimates from the southern hemisphere for their 2016

10 season.

11   The other thing that we're now incorporating is

12 several modelers who are doing viral fitness forecasting.

13 They're taking our genetic data, and we're in a process of

14 also folding our antigenic data in, in an effort to try and

15 predict what the next emerging variant may be. But these

16 data are only as good as the data that we have available at

17 the time, so that's constantly the struggle, and even the

18 modelers are recognizing that it's pretty hard to predict

19 what's going to happen this time next year.

20   And then also we heard from CBER, they had some

21 neuraminidase antigenic characterization data. So more to

22 come on that.

23   So I'd just like to acknowledge all of the

24 collaborating centers for all the work I've presented as

25 well as the National Influenza Centers without whom we

1 wouldn't have these viruses to begin with, our Cambridge

2 partners for antigenic cartography, and our many U.S.

3 partners, particularly our partners at DoD that provide

4 critical genetic information. And of course our CDC

5 colleagues in Atlanta.

6   Thank you.

7   DR. EL SAHLY: So the story with the influenza B

8 has been around 50/50 for a few years now, and it seems to

9 be continuing that way, give or take. And given that the

10 vaccine, quadrivalent versus trivalent, is also around 50

11 to 60 percent, the choice of Victoria not changing over

12 different seasons -- I'm thinking about what would be a

13 benefit, or if it would be of a benefit, to include the

14 Yamagata on subsequent seasons. You know what I mean?

15 Like, alternate, or if the story is continuing to be 50/50,

16 and our coverage of quadrivalent is still not moving fast

17 enough --

18   DR. KATZ: It's not always 50/50. I would say

19 that several seasons ago we had predominantly B/Yamagata.

20 Last season in North America at least we saw an increase of

21 B/Victoria, and that continued but didn't take over the

22 B/Yamagatas. But in other regions of the world there has

23 been more B/Victoria, and really the decision that the

24 group made last week was -- and it was a tough decision --

25 but we really considered the countries and the regions

1 where B/Victoria was still predominating, and we heard that

2 they were regions of the world that were more likely to

3 have only trivalent inactivated vaccine. We know in -- it

4 was probably around 60 percent usage in the United States

5 this year. It may increase.

6   And in other regions like Australia they are

7 moving totally over to quadrivalent. So when some of the

8 more European, Australia, U.S. countries, there is this

9 move to quadrivalent. So we felt that the decision for

10 trivalent should be focused more in regions where they

11 didn't have access to quadrivalent vaccine. That was one

12 reason that we made that selection.

13   Also I think -- and we looked at past VE data, we

14 looked at how the viruses have changed, as you say, from

15 season to season, the epidemiology, and it was really very

16 difficult to come up with a pattern that -- we can't

17 predict if B/Victoria or B/Yamagata will be predominating

18 next season, at least in North America or anywhere else.

19 We expect both will be circulating.

20   DR. EL SAHLY: So, given that the bulk of

21 individuals who receive -- everybody who got trivalent last

22 year, we can predict that they may be partially protected

23 against Victoria next year, partially. But we did not use

24 trivalent Yamagata, and it seems to be 50/50 or 40/60 every

25 year. You know what I'm getting at with this?

1   DR. KATZ: I think so, but I really think it's

2   hard to pin what we're seeing epidemiologically with what's

3   in the vaccine. We do know the B/Victoria this year, as we

4   were seeing last season, that it's largely people under the

5   age of 25 that are getting infected with B/Victoria.

6   DR. MONTO: I was going to say the good news is

7   there's a lot more cross-protection between the lineages

8   than we originally thought. When decisions were made to go

9   over to quadrivalent vaccine, one wonders whether those

10   decisions would have been the same if we had had some of

11   our VE studies that we've had recently.

12   My question is about 3C.2a1. Because I have

13   reviewed some papers from Europe which say that vaccine

14   effectiveness has gone down since 3C.2a1 strains have come

15   in. There's clearly cross -- in terms of antigenic

16   cartography, they cluster together. Are some of these

17   outliers, the ones that have lost glycosylation sites and

18   the rest, are they responsible, or is this just early

19   numbers in terms of some of the studies? Some of the

20   studies from Europe have had really small numbers and

21   almost ecologic conclusions about why they were seeing

22   these drops.

23   DR. KATZ: Yeah, I would agree. We will do the

24   subclade analysis when we have our final data. Obviously

25   that's not helpful here. But for the Canadian studies they

1 did do a breakdown of VE against 3C.2a1, and it was

2 similar. I think it was about 43 or 44 percent, which was

3 what their overall H3N2 VE was, similar to what we saw in

4 the United States.

5   I think some of the other studies that are coming

6 out, and there are some studies from Europe that are naming

7 new genetic groups, there's a group that are calling

8 something 3C.2a2, and the WHO group hasn't really -- we

9 recognize the group they're seeing, but it's a very local

10 circulation of particular viruses, and I don't know that we

11 can really ascribe too much to the VE that is being seen

12 because of the small numbers when they break it down.

13   Certainly in our panels of post-vaccination human

14 sera, we saw that antibody elicited by the 2a virus, Hong

15 Kong/4801, reacted just fine with the 3C.2a1 viruses we

16 tested in multiple labs.

17   DR. BENNINK: The 2a2 -- that was the one -- they

18 had two clusters, but wasn't there one of these that had

19 the glycosylation change?

20   DR. KATZ: Yes, it was within the 3C.2a group, and

21 it had a change at 144. So it was one of the groups I

22 highlighted.

23   DR. BENNINK: Which then, if that takes off,

24 that's really going to be a major change.

1   But do you have any potential candidate vaccines,

2   do you have anything like that, that in your antigenic

3   cartography, centers more within what's circulating,

4   whether they're 2a or 2a1, whatever it is, because the

5   virus that we're using here, is kind of off to the side

6   some. Do you have anything that's a potential candidate

7   vaccine that's more centered?

8   DR. KATZ: So, a couple of candidate vaccine

9   viruses are in development, for 3C.2a1. I did point out

10 one that was developed here. CDC sent a virus, Alaska/232,

11 for reassorting, and its antisera I showed you in an HI

12 really poorly covered circulating viruses. So we really

13 just don't think that's a good candidate. There's another

14 candidate that is under development, but there's just not

15 sufficient data to say whether it would be better or worse

16 than the Hong Kong/4801 virus.

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

18   DR. KATZ: The one I mentioned. There is another

19 European virus that several of the reassorting labs have at

20 present, but it's months away probably from having a

21 candidate.

22   PARTICIPANT: But the Brisbane is not very far? I

23 think there was one, Brisbane?

24   DR. KATZ: For H3N2?

1   PARTICIPANT: Yeah, I thought so, but maybe I'm

2   wrong. I thought you had a slide there. But the ones in

3   Europe, is that Bolzano? Or is that Scotland? Or

4   something else?

5   DR. KATZ: There's a Norway virus that has gone to

6   several reassorting labs, and I think I -- in one of the

7   neutralization tables they had antisera raised to the cell-

8   propagated Norway virus, and it covered quite well. The

9   question always is what's it going to do in eggs?

10   DR. GREENBERG: Perhaps you answered my question

11   about the 3C.2a and 2a1, but I was curious as to why -- and

12   I see the data -- but I was a little bit surprised that

13   there isn't a better match with the 3C.2a1, because as was

14   just said, that's the circulating strain. So I would have

15   thought just intuitively, that a strain for vaccine that's

16   a 3C.2a1 would be a better antigenic match to the 3C.2a1

17   circulating strain.

18   DR. KATZ: We're not seeing that in our antigenic

19   data. We're really seeing the antisera to the Hong

20   Kong/4801 covers these viruses just as well -- the 2a1's

21   just as well as the 2a viruses.

22   DR. GREENBERG: And I have a follow-up question

23   about the B lineages. I was struck that for North America,

24   most recently, say January of 2017, you did show that there

25   was an uptick of the Yamagata, and you know again, it'll be

1 a difficult decision for the committee. Does that --

2 should the committee consider that in deciding which should

3 be in the trivalent and which should be in the

4 quadrivalent?

5   DR. KATZ: I can only give you the example of the

6 H3N2s last season, where we saw quite an uptick of 3C.3a's

7 and we were really concerned that -- and that was at the

8 end of the season, and we'd already made the selection of

9 Hong Kong/4801, which is a 2a, and there was concern that

10 maybe this season we'd see 3C.3a's, and they just went

11 away. We saw a few of them, but not many, so it's really

12 hard to predict.

13   DR. GREENBERG: Okay, thank you. Just one final

14 question about the B. I noticed on the phylogenetic tree

15 that the B/Brisbane is a bit far from the current

16 circulating strains, but yet the antigenic and the ferret

17 sera seem to work out.

18   DR. KATZ: There just haven't been that much

19 genetic diversity in the Bs. They tend to evolve a little

20 more slowly. And we haven't seen the impact on the

21 antigenicity. We do continue to make new candidate vaccine

22 viruses to that group, but we haven't found anything that's

23 performing better than the Brisbane.

24   DR. MOORE: I was really struck by your data on

25 the microneuts that you showed for the Hong Kong 3a strain,

1   the H3 strains. It's a yellow slide, and it shows cell

2   versus egg, virus -- four different participating centers

3   that did microneuts. And I always think that neuts are

4   much better than hemagglutinin inhibition assays for

5   actually telling us whether the vaccine will be effective

6   in giving us sterilized immunity for infection. So perhaps

7   it's a good thing that this virus doesn't have a very good

8   HI activity.

9   But here what we're seeing, if I understand this

10 correctly, is the egg-derived strain, which is the same way

11 that most vaccines are made, is giving only coverage to

12 about 19 percent, and so it's a complete disconnect from

13 the cell-based, whereas you don't see that for any of the

14 other, for the B virus, and the H1.

15   DR. KATZ: Right, and as I alluded to, but

16 probably didn't explain specifically -- and we can use the

17 CDC data as an example -- so we get very good concordance

18 when we use antisera raised to cell, but our antisera

19 raised to the egg-propagated Hong Kong/4801-like virus has

20 an extremely high homologous titer, and unfortunately I

21 don't have an example.

22   So this isn't an extremely high homologous titer,

23 but this is data from the Crick London collaborating

24 center. But you can see that there's more 40s and 80s with

25 egg-propagated by neutralization. With our data we have a

1 titer that is -- for our antisera -- that is thousands,

2 it's over 5,000. So even though we're getting reasonable

3 titers, that difference is just so much greater that we

4 have to call them, that they're low reactors.

5   So it's a property of the egg viruses, both how

6 they perform, and an example of that is -- so in

7 neutralization tests, this is human sera, but you can see

8 we're getting extremely high titers whenever we use egg

9 sera. So what we're doing in the HI or the neutralization

10 we're taking sera raised to egg-propagated viruses, and

11 sometimes these egg adaptations confer properties on the

12 virus and the antisera that cause very high homologous

13 titers. And we're always comparing to cell-grown viruses

14 that always have a lot lower reactivity. So it's a

15 struggle. But you're right, there is that problem.

16   DR. MOORE: So, does that help us? I guess what

17 you're saying is, because egg titers have such a high titer

18 neutralization, then your non-homologous neutralizations

19 are going to be manifold lower, and are going to look

20 lower, but they're still effective neutralizations, is what

21 you would predict. However, we know the vaccine efficacy

22 for this strain against virus that we're seeing is not that

23 great, and it's likely to get worse.

24   DR. KATZ: It's not great. I think the best we

25 can do right now is match the vaccine strain as close to

1 the circulating strain as possible, then the current year's

2 data and past data suggest we'll be around 40 percent. Is

3 that satisfactory? No, it's not. We need to do better for

4 the H3N2s.

5   DR. MOORE: I guess my question then is,

6 apparently there is new MDCK-derived vaccine that's been

7 approved. Is that right? I'm not clued in to that.

8   DR. KATZ: So one company that is licensed in the

9 United States, and FDA may want to jump in, produces the

10 vaccines in a proprietary MDCK cell line, and last year FDA

11 approved that the seed virus, the starting material, can

12 also be grown in cells. Prior to that, even though the

13 vaccine was manufactured on a cell platform, they still had

14 to start with an egg-grown virus. And if you start with an

15 egg-grown virus you've still got those egg adaptations.

16   Now FDA has agreed or approved the use of a cell-

17 propagated seed virus. And so we hope that as these

18 changes -- as recommendations are made -- that cell-based

19 candidate vaccine viruses will be used in the future, and

20 will overcome that egg issue. For that vaccine only.

21   DR. MOORE: So we don't actually have the neut

22 titers here. We just have the differences in eightfold and

23 not within each group. But I guess what I'm trying to get

24 a feeling in my own mind is, is it likely that the cell-

1 grown virus will have better neutralization activity and

2 hence better vaccine efficacy for the Hong Kong strain?

3   DR. KATZ: We can't say. And unfortunately, it's

4 not a major proportion of the vaccine that's used, so as

5 Lisa mentioned, it's very difficult to get vaccine type-

6 specific information because of the variety of vaccines

7 that are used in the United States. But my understanding

8 is that that is still -- and maybe the manufacturers want

9 to address that -- but I'm not sure what proportion of the

10 U.S. market that would represent. But it's small.

11   Overall, the majority of flu vaccines are still

12 egg-based, more than 90 percent. A small proportion of the

13 market is the recombinant HA, which could again potentially

14 overcome the egg issue and the cell-based product.

15   DR. EDWARDS: Thank you, Jackie. I think for now,

16 time for a break. We're about 15 minutes late, but I think

17 we can still have a 15-minute break, maybe 20 minutes.

18   (Break.)

19   **Agenda Item: DoD Vaccine Effectiveness Report**

20   DR. EDWARDS: The next report will be the DoD

21 Vaccine Effectiveness Report given by Dr. Michael Cooper of

22 the Respiratory Infection Surveillance Global Emerging

23 Infection Section of the Armed Forces Surveillance Branch

24 in Silver Springs. Dr. Cooper.

1   DR. COOPER: Thank you. This is my disclaimer.

2 So, good morning. As is mentioned, my name is Michael

3 Cooper, and I am the lead for Respiratory Infection

4 Surveillance with GEIS, which is the Global Emerging

5 Infection Surveillance section of the Armed Forces Health

6 Surveillance Branch. We are a DoD asset. Today I will be

7 presenting data from the 2016-2017 season midyear report

8 from our Influenza Surveillance Network.

9   Included here will be surveillance data from our

10 partners in North America, South America, Asia, Africa, and

11 Europe, as well. In addition, surveillance data will also

12 be presented on military recruits here in the United

13 States. I will also be presenting a brief summary on

14 phylogenetic analysis developed by our partners at the

15 United States Air Force School of Aerospace Medicine, also

16 referred to as USAFSAM.

17   In addition, I'll be presenting three midyear

18 estimates of vaccine effectiveness developed by the Naval

19 Health Research Center in sunny San Diego and USAFSAM in

20 not-so-sunny Dayton, Ohio, and the Armed Forces Health

21 Surveillance Branch right down the road in Silver Spring.

22   I just want to take a moment to give you a little

23 background on my organization and our influenza

24 surveillance network. Again, we are a DoD asset and we're

25 dedicated to surveillance of infectious diseases primarily,

1 but not exclusively, in military populations. Our

2 influenza surveillance program extends to over 30 countries

3 and has over 400 sites in those countries.

4   In addition to monitoring United States military

5 infectious disease, we have partners who have relationships

6 with foreign governments, ministries of health, ministries

7 of defense, which provide disease surveillance data on

8 local and national populations. On average our network

9 collects and analyzes about 30,000 influenza or respiratory

10 samples per year and send between 300 and 400 sequences to

11 GeneBank each year.

12   Here is a map of where we are in the world.

13 You'll see the blue spots are countries where we have

14 surveillance, either local national populations or

15 military. You'll also see some red dots there. They are

16 embassies that we also have in our network who can send

17 samples to us whenever they need to.

18   The first graph I am going to share with you is

19 on United States military recruits. These are individuals

20 going through basic training. Basic training usually lasts

21 anywhere from two months to thirteen weeks depending on the

22 service. About 180,000 individuals go through basic

23 training each year. It is a rigorous process. It's a very

24 stressful, sleep-deprived process.

1   Along the X axis, you'll see are epi weeks.

2   You'll see there are three years' worth of data there for

3   comparison. Along the Y axis on the left-hand side, you'll

4   see it is the number of specimens tested, and the Y axis on

5   the right-hand side is the percent positive.

6   It's an interesting group to do surveillance on,

7   especially for respiratory disease. Historically, up to 20

8   percent of a recruit class could be hospitalized for

9   respiratory infections. They are very much at risk. They

10 are also a highly-vaccinated population -- 100 percent

11 vaccination for influenza, also 100 percent for various

12 other viruses as well.

13   If you take a look here, you'll see this is

14 adenovirus -- that's what I was searching for, sorry --

15 you'll see that we're color coordinated regarding our

16 influenza subtypes, H3 being the green, H1 being the blue,

17 and dark blue is influenza B. If you look at the far-right

18 hand side, you'll see that this data goes out through

19 February and it is primarily H3N2 season that the recruits

20 are experiencing -- little bit of influenza B.

21   What's interesting to look at in addition is --

22 if you look in July and August timeframe, weeks 20 and 31,

23 or 16 and 19 in May, you're seeing spikes in influenza and

24 that's not terribly unusual in the recruit classes. This

 1 highlights the need for year-round surveillance in this

 2 particular group.

 3   These data are from North America. These are

 4 active duty military members and dependents. Also a select

 5 civilian population near the Mexico-California border.

 6 Again, relatively mild season, H3N2 by and large.

 7   In Europe, we have about 190,000 individuals in

 8 Europe, about a third of that being active duty military,

 9 the rest being family members and dependents. And you can

10 see, by and large, they are seeing H3N2 as well. The

11 countries covered in this surveillance are our U.S.

12 military members and family members stationed in Germany,

13 United Kingdom, Turkey, Spain, Italy, Belgium, and

14 Portugal.

15   Our data from Latin America comes from Peru,

16 Paraguay, Columbia, Nicaragua, and Honduras. It is a mix

17 of U.S. military members and local national populations.

18 Of course, these countries fall within a tropic band, so

19 you wouldn't expect a flu season, per se. Looking at the

20 most recent data, you'll see influenza B and H3N2

21 represented.

22   These data come from our partners in Asia and

23 countries represented here are Nepal, Philippines, Bhutan,

24 Indonesia, Cambodia, Korea, Japan, and Thailand. You're

25 probably aware that we have sizable military populations in

1 Japan and Korea, so this is a mix of local national

2 populations and U.S. military. As you can see, the far-

3 right hand corner, it's a mix of H3N2, Flu B, and some not

4 subtyped. Again, these countries fall within a tropic

5 zone, so you wouldn't expect a flu season at this point.

6   These data come from East Africa. It's Kenya,

7 Uganda, and Tanzania. The most recent data for the past

8 few months is a mix of H3 and H1 with some influenza B as

9 well.

10   In summary regarding our circulating strains in

11 surveillance, North America and Europe, military members

12 and dependents have experienced low to moderate flu

13 activity so far. Positive samples have been primarily

14 H3N2. Globally, there is a mix of H3N2 and H1 with some

15 influenza B as well.

16   Now I am going to present to you some

17 phylogenetic analyses and to start off with, I think it's

18 fair to say that the majority of these analyses were

19 reported on; they're a subset of Dr. Katz's analysis with

20 the exception of some of the more recent sequences obtained

21 on H3N2. So I will probably go rather quickly through H1N1

22 and the Bs and concentrate a little bit more on H3N2 for

23 the sake of time.

24   This graph here gives you some idea as to where

25 in our network our sequences have come from. The map shows

1   -- well, for these analyses, 412 sequences were collected.

2   83 percent of those were influenza H3N2, 5 percent were

3   influenza H1N1, and 10 percent were influenza B/Victoria,

4   and 3 percent were influenza B/Yamagata. These sequences

5   come from 16 countries over five continents. The H3N2 was

6   the predominant subtype in all regions except for in Africa

7   and East Asia, where B/Victoria was either equal to or

8   greater than the number of sequences for H3N2. And that's

9   just a summary of basically what I just told you.

10   So looking at H1N1, all 19 of the H1N1 sequences

11 collected were in clade 6B; 79 percent of those were in

12 subclade 6B.1. The component that is recommended is

13 A/Michigan/45/2015-like virus. Looking at the H3N2

14 phylogenetic analysis, 150 of the 341 H3N2 sequences

15 collected from 2016 through 2017 so far were selected to

16 represent clade proportions as well as geographical and

17 temporal distributions.

18   About 7 percent of the sequences were in clade

19 3C.3a, 65 percent were in 3C.2a1, and 11 percent were in

20 the proposed clade, 3C.2a2, while 16 percent were in 3C.2a

21 with no further subclade designation. The recommended

22 component for the 2017-2018 vaccine is A/Hong

23 Kong/4801/2014-like virus.

24   I won't spend a lot of time on this graph, it's

25 just there to demonstrate the genetic dynamic nature of

1 H3N2. You'll see that this is from July to January looking

2 at amino acid substitution. You'll see in the top two,

3 N171K and N121K, lots of substitutions. Go down to 158V,

4 little to none. So again, this is just designed to

5 highlight the dynamic nature of H3N2, as Dr. Katz already

6 has.

7   Looking at influenza B/Victoria, all 39 of the

8 influenza B/Victoria sequences were from clade 1A. Three

9 strains were found to have a deletion at amino acid

10 positions 162 and 163. The recommended component for the

11 2017-2018 vaccine is either B/Texas/02/2013-like virus or

12 B/Brisbane/60/2008-like virus.

13   Finally, looking at B/Yamagata, all 13 of the

14 influenza B/Yamagata specimens were in clade 3. The

15 recommended component of the quadrivalent vaccine is

16 B/Phuket/3073/2013-like virus. There is a summary in your

17 handouts, so you can refer to those.

18   As I mentioned, I'm going to present information

19 on three vaccine effectiveness studies. As I've mentioned,

20 to this point, the flu season has been relatively mild in

21 most regions covered by the DoD influenza network. In some

22 instances, there is not enough cases for detailed sub-

23 analyses. The analyses have been somewhat simplified, due

24 to the fact that LAIV is not being used and the fact that

25 there is too little H1N1 in some cases -- well, actually,

1   in all cases -- to look specifically at the vaccination

2   effect for H1N1 specifically.

3   So these midyear estimates are provided by the

4   United States Air Force School of Aerospace Medicine, Naval

5   Health Research Center, and Armed Forces Health

6   Surveillance Epi and Analysis section. Each uses the case-

7   control method. Each uses logistic regression to estimate

8   the vaccine effectiveness, or to estimate the odds ratio,

9   which is then used to calculate the vaccine effectiveness.

10 Two studies used control-test negative method, and the

11 study conducted by the Epi and Analysis group at the Armed

12 Forces Health Surveillance Branch used Health Controls

13 rather than test negative controls.

14   No analyses by H1N1, I should say. Again, it was

15 an H3 dominant season. Each influenza infection was

16 confirmed by PCR or viral culture. And here is our testing

17 criteria, which is a little bit different from CDC's. We

18 still use fever of 100.5 as one of the criteria. Cough and

19 sore throat, and the specimens should be collected within

20 72 hours of the onset of symptoms.

21   These analyses look specifically at healthcare

22 beneficiaries, not active duty members. So it is the

23 children and spouses of military members. The time period

24 is from October 12, 2016 through February 18. The analysis

25 was by influenza subtype, H3N2 and B, and by age group,

1 children versus adults -- those under 18 versus those above

2 18. Adjusted for age, month, and illness. Statistically,

3 we had 534 cases, that comes down to about 477 after

4 missing data are accounted for. These cases again were

5 confirmed by PCR or viral culture, and we were able to come

6 up with 838 test negative controls. This is far from

7 optimal. This is about 1.5, 1.6 controls to cases.

8 Usually, you'd like 4:1.

9   Vaccination rates, about 32 percent of cases were

10 vaccinated, and 36 percent of controls were vaccinated. 89

11 percent of the cases were H3N2, 1 percent was H1N1, and 10

12 percent influenza B. Here is your age breakdown. Again,

13 60 percent of our cases were under the age of 18. About 40

14 percent were over. And a slightly finer look at the age

15 distribution, and you can see that about 18 percent were

16 over the age of 50.

17   So the adjusted estimate for vaccine

18 effectiveness. H3N2 overall adjusted VE was moderately

19 protective and statistically significant for influenza

20 H3N2. VE was 42 percent. This was statistically

21 significant for children, not so for adults. Again, 60

22 percent of our cases were under the age of 18.

23   For flu B, the overall adjusted VE was moderately

24 protective and statistically significant for influenza B, a

25 VE of 53 percent. When looking at this, it was looking at

1 all flu Bs, but about 77 percent of those with influenza B

2 were under the age of 18. So the vast majority were

3 children.

4   Here are your adjusted estimates of vaccine

5 effectiveness, confidence intervals, and your VE estimates.

6 You can see that the all dependents, vaccinated versus

7 unvaccinated, 42 percent vaccine effectiveness, with a

8 confidence interval of 24 to 56. Looking at adults, just

9 the individuals above the age 18, or 18 or over, you have a

10 VE of 32 percent. It's not statistically significant. And

11 looking at individuals under 18, you have a vaccine

12 effectiveness of 48 percent. Looking at all influenza Bs,

13 you have a vaccine effectiveness of 53 percent. That is

14 statistically significant.

15   The next estimate of vaccine effectiveness I'm

16 going to share with you, the population used in this study

17 was DoD dependents in Southern California, Arizona, and

18 Illinois outpatient clinics and civilians near the U.S.-

19 Mexico border, specifically the California-Mexico border.

20   These analyses are adjusted for study

21 populations, military dependents versus Mexico border

22 civilians. Only obtained 75 cases, which is the lowest

23 I've seen since I've been involved with this work, and

24 that's several years. It's usually in the neighborhood of

25 150 or so, or 130, so not much in the way of sub-analysis.

1 We weren't able to do many sub-analyses with such a small

2 number of cases. Each of those cases was confirmed by RTC-

3 PCR.

4   Selected 224 test negative controls for a 3:1

5 ratio. The vaccination rates for cases was 33 percent,

6 controls 48 percent. 93 percent of the cases were H3, 4

7 percent were flu B, and 3 percent H1N1. Almost, well, 68

8 percent, almost 70 percent of the cases, were under the age

9 of 18, and about 30 percent of the cases were between the

10 ages of 18 and 64, with no one above the age of 65.

11   So the VE for H3 was moderately protective and

12 statistically significant. When parsing it out by age

13 group, for children, the VE was -- the point estimate was

14 moderately protective but it was not statistically

15 significant. And here is the odds ratios and the VE

16 internals for that analysis, about 46 effectiveness for

17 all. Again, we're running into statistical power issues

18 here.

19   Now this analysis is for active duty members

20 only. And rather than using the test negative controls, we

21 use health controls, and again these are Army, Air Force,

22 Navy, Marines, and Coast Guard members, both located within

23 the United States and outside of the United States. There

24 were 987 lab-confirmed cases, and these are confirmed by

25 rapid test, PCR, or culture.

1   There were 3,709 health controls selected. These

2   were individuals with medical encounters for injuries or

3   mental health conditions, with no ILI reported at the

4   encounter, and no medical encounters for influenza during

5   this flu season. And they were matched to cases by sex,

6   age, date of encounter, and location.

7   The models also adjusted for a five-year

8   vaccination status. And that's a dichotomous outcome, yes

9   or no? So we'll probably talk about that a little bit more

10 later.

11   Obviously we're dealing with a truncated age

12 distribution here. You're not going to see people under

13 the age of 17 certainly, and you're probably not going to

14 see many people above the age of 60 in the active duty

15 population. And so here's the distribution: 91 percent of

16 cases were vaccinated; 89 percent of controls were

17 vaccinated. You can see there's going to be problems in

18 trying to calculate an odds ratio here. It's really

19 difficult to find a vaccinated case, or an unvaccinated

20 case I should say, under these circumstances.

21   Six hundred and thirty-six of the influenza As

22 were unsubtyped. They tend to come from clinical areas

23 that don't do subtyping, 261 of the H3N2s, or I should say,

24 influenza H3N2, there were 261 cases. And only 12 H1N1s,

25 and 79 influenza Bs. Ninety-three percent of the cases and

1   95 percent of the controls had prior vaccine in the

2   previous five years.

3   And obviously we're very well matched, cases to

4   controls. The majority of your cases, about 37 percent,

5   are between 30 and 39. And 18 to 24, there's about 30

6   percent of your cases are between 18 and 34.

7   Estimates for influenza A, the VE estimates are

8   very low, and not statistically significant. We have wide

9   confidence intervals, low power due to relatively small

10   numbers and very high vaccination rates. For flu B numbers

11   were too small to produce reliable estimates, so we don't

12   include any in this presentation.

13   And here are your vaccination estimates. VE

14   estimates, as I should say: 3 percent for influenza A, 33

15   percent for influenza H3N2.

16   And this is a summary of everything I've

17   presented here. Again, for dependents and civilians

18   overall the VE for H3N1 was moderately protective and

19   statistically significant. VE against flu B was moderately

20   protective and statistically significant in the USAFSAM

21   analysis. For active duty military members, VE was not

22   statistically significant for influenza A. So, our

23   limitations.

24   Obviously, these individuals were sick enough to

25   seek medical attention. So we can't really comment on

1 vaccine impact for less severe cases. Active duty military

2 members are highly immunized. This could have a negative

3 impact on VE, potential methodological issues, power, and

4 potential biological effects such as an attenuated immune

5 response with repeated exposures.

6   The populations in this work are younger, so we

7 can't really comment on vaccine impact in older, high-risk

8 populations. USAFSAM analysis was limited by a suboptimal

9 control-case ratio, but yet they found statistical

10 significance for H3N1 and for B. So the effect size must

11 be rather robust.

12   The NHRC analysis, we're limited by very small

13 numbers. Only 75 cases. And the Armed Forces Health

14 Surveillance Branch analyses were limited by high

15 vaccination rates, low statistical power, and other

16 potential issues.

17   I'd like to thank our partners from basically

18 throughout the world. And I'm happy to take any questions.

19   DR. EDWARDS: Questions?

20   DR. MONTO: The first VE analysis, there was a

21 rather a large difference between the unadjusted and the

22 adjusted rates, unlike the next one, which looks more like

23 what we usually see. Is there any explanation for why the

24 crude and the adjusted were so different?

1   DR. COOPER: I could only offer a guess, and

2   that's I would imagine it has to do with the differences in

3   the proportion to gender. These are, again, dependents.

4   These are not active duty members.

5   DR. MONTO: The next group was pretty close.

6   Again with the same point estimates. Very curious.

7   DR. COOPER: Very different populations, case

8   sizes as well, and the fact that -- this one here, this is

9   the second one you're talking about?

10   DR. MONTO: Yeah. This is more like what we're

11   used to seeing.

12   DR. COOPER: Well, it could have to do with

13   unanalyzed confounders, or some interaction that's been

14   untested.

15   DR. JANES: Related to that point, I was going to

16   ask who the controls were for these first two studies. You

17   know, how comparable are the cases and controls, and big

18   differences between the groups could explain --

19   DR. COOPER: For the first study, the controls are

20   also military dependents, spouses and children. For the

21   second they are all -- for the NHRC study they are all

22   again, military members, and individuals who use a clinic,

23   a number of clinics on the California border. So they're

24   all selected from the same populations. And in addition,

25   which the NHRC analysis, they do what they could

1   statistically to try and control for whether they were

2   military or border, by putting that in the model.

3   DR. EDWARDS: I thought your inter-influenza

4   season data were interesting. So you do see a lot of

5   clustering of influenza in non-influenza seasons in the

6   recruits. Could you talk a little bit about that? What

7   strains are they, do they come from southern hemisphere, or

8   sort of what are your thoughts about that?

9   DR. COOPER: Well, if we go back to the original,

10 what we saw last summer was H3N2. That's not always the

11 case though. In this particular case, it's not unusual to

12 see little spikes, and sometimes large spikes, of

13 respiratory infection during the summer months. You have

14 people coming from all over the country, with varying

15 immune profiles, varying experiences with viral infections,

16 being put together in close confines under a lot of stress.

17 So many, all sorts of things become problematic. Generally

18 speaking we don't see a lot of adenovirus in the civilian

19 population. But you see plenty of adenovirus -- before we

20 had the vaccine back, it came back in 2011 -- you were

21 seeing very large numbers of adenovirus and high numbers of

22 hospitalizations as well. So it's a very unique kind of

23 population.

24   DR. EDWARDS: The next discussion will be on

25 candidate vaccine strains and potency reagents, by Dr.

1 Joshi, lead biologist at the Divisions of Biologic

2 Standards and Quality, Office of Compliance and Biologics

3 Quality at CBER, FDA. Dr. Joshi?

4 **Agenda Item: Candidate Vaccine Strains and**

5 **Potency Reagents**

6 DR. JOSHI: Good morning, everybody. I am Manju

7 Joshi, and I work in the Division of Biological Standards

8 and Quality Control in the Office of Compliance and

9 Biological Quality at CBER. The Division of Biological

10 Standards and Quality Control -- we call it DBSQC to short,

11 it's too long a name -- in collaboration with other

12 essential regulatory laboratories, participates in

13 generation and calibration of reagents required for testing

14 of influenza vaccine.

15 Our division also manages and provides these

16 reagents for all the U.S. licensed manufacturers. In this

17 presentation I will give you an update on the candidate

18 vaccine strains and go over our division's goals towards

19 preparing and supplying influenza vaccine testing reagents

20 for the 2017-2018 season.

21 In my presentation I will go over currently used

22 vaccine strains and WHO recommendations for 2017-2018

23 seasonal vaccines, both trivalent and quadrivalent. I will

24 also update you on the status of available reagents for

25 each of these strains, and I'll make some general comments

1 which will be not so much for committee, it will be for the

2 other members in the audience, especially the industry

3 representatives.

4   Coming to the influenza A of H1N1 type. For H1N1

5 type, the current vaccine strains was A/California/07/2009-

6 like virus. A number of reassortants have been used in the

7 manufacture of vaccine last season. This included X-179A

8 and X-181 reassortant for A/California/7/2009 and NIB-74

9 and NIB-74xp for A/Christchurch.

10   And I'm sorry, I'm just not going to say all the

11 numbers because they're too long, so we'll just restrict

12 ourselves to a short name.

13   And at the same time, A/Brisbane/10 and another

14 A/California-like virus was also used in vaccine

15 manufacturing. Last season CBER provided reagents for egg-

16 derived A/California X-179A and X-181 reassortant.

17 Similarly NIBSC UK had provided reagents for NIB-74

18 reassortants as well as A/Brisbane/2010 wild type cell-

19 derived virus.

20   The WHO has recommended the strains for 2017-18

21 and I think by now each speaker has gone over it, and we

22 know that the recommendations comes as A/Michigan/45/2015

23 (H1N1)pdm09-like virus. Given here is the list of

24 candidate vaccine viruses that has been recommended for

25 this group. And as all of you know in this audience, that

1   this strain also been recommended for 2017 southern

2   hemisphere season.

3   Coming to the status of the reagents. This is

4   provided. We all understand that inclusion of WHO proposed

5   strains in the vaccine is based on the approval by the

6   committee today. If this strain gets approved, we'll just

7   take a look at where we stand in terms of the reagents.

8   Let me point out that CBER is in the process of

9   getting reagent ready for A/Michigan/45/2015 X-275

10 reassortant. The antiserum preparation is ongoing, and as

11 soon as antiserum is ready, the calibration of reference

12 antigen will be initiated.

13   Since this strain was recommended for southern

14 hemisphere campaign, NIBSC had prepared reagents for

15 A/Michigan/45 X-275, while for A/Singapore/GP1908 IVR-180,

16 reagents were prepared by both TG Australia and NIBSC UK.

17   TGA worked and have already prepared a cell-

18 derived reagent for A/Singapore/GP1908. Please note, again

19 this is more for the audience part, please note that CBER

20 will authorize use of reagents from other ERLs if this

21 strain is selected today, and this will be on a case-by-

22 case basis, and we really request the industry

23 participants, representative, to get the feel that we would

24 like you to consult with DBSQC prior to using any reagents

25 from other ERLs.

1   Coming to the H3N2 strain, for 2016-2017 season,

2 A/Hong Kong/4801/2014-like virus was recommended. A/Hong

3 Kong/4801 and its reassortant X-263 were used for vaccine

4 manufacturing. SRID reagents for the potency-testing

5 reagents for egg-derived X-263B reassortants were made

6 available by CBER as well by NIBSC. Reagents for cell-

7 based A/Hong Kong strain were prepared by CBER and

8 provided.

9   This year, as all of you know, that WHO has

10 recommended there be no change in this strain for 2017-2018

11 season, and a number of candidate vaccine viruses, both the

12 egg-derived and cell-derived, have been proposed. I'm not

13 going to read any of these names in the interest of time,

14 and we all know that the same strain has also been

15 recommended as an H3N2 strain for 2017 southern hemisphere

16 season.

17   If this strain is selected by the committee

18 today, here is the status of the reagents. For A/Hong Kong

19 X-263B reassortant, which was used last year in vaccine

20 manufacturing as well, CBER had prepared reagents and those

21 reagents are still available. Similarly reagents for the

22 same 263B strains are also available from NIBSC and TGA.

23   Reagents for reassortant X-263 were prepared were

24 prepared by NIAID last year and they are available. In

25 addition, reagents for A/New Caledonia/71 reassortant were

1 prepared by TGA last year and they are still available.

2 Last year CBER had prepared reference reagents for cell-

3 derived A/Hong Kong, and we still have those reagents

4 available. As far as antiserum lot, we usually get

5 depleted over a period of time faster than anything.

6 Currently we have two lots of antiserum available for

7 vaccine testing, and preparation of additional antiserum

8 lots for testing are planned in coming months.

9   And again, I don't have to say again, the blue

10 words say, please consult.

11   Coming to the influenza B virus from Victoria

12 lineage. For 2016-2017 northern hemisphere season, WHO had

13 recommended that the B strain for trivalent quadrivalent

14 vaccine B be B/Brisbane/60/2008-like virus from Victoria

15 lineage. Last year, wildtype B/Brisbane/60 and B/Hong

16 Kong/259/2010 viruses were used in vaccine preparation. A

17 number of reagents were made available for different

18 B/Brisbane/60-like candidate vaccine viruses.

19   For testing of egg-derived product prepared using

20 B/Brisbane/60 reagents were provided by CBER, NIBSC, and

21 TGA, and predominantly CBER reagents were used in testing.

22 Similarly reagents for cell-derived B/Hong Kong were

23 provided by CBER. Again, no change has been recommended by

24 WHO for this B strain for either trivalent or quadrivalent

1 vaccine, and, again, their recommendation is to continue

2 B/Brisbane/60-like virus as the B component in the vaccine.

3 Again, I'm not going to read all, but there are a

4 number of egg-derived candidate vaccine viruses, they are

5 both wildtype as well as the reassortants which have been

6 prepared, as well as cell-culture derived viruses of this

7 group are available. Again, this recommendation was made

8 even for the southern hemisphere 2017 campaign.

9 If today committee selects this strain, let's go

10 over the status for the reagents we have available for

11 vaccine testing. So, egg-derived antigen for B/Brisbane/60

12 is available from CBER. Egg-derived reagents for

13 B/Brisbane/60 is also available from NIBSC and TGA.

14 Reagents for the reassortant BX-35 are available from NIBSC

15 as well. Again TGA has reagent available for another

16 B/Brisbane/60-like virus which is B/Brisbane/46, and NIAID

17 Japan has reagent for B/Texas/2/2013 virus.

18 CBER had last year prepared cell-derived reagent

19 for B/Hong Kong/259 and that is available. CBER also has

20 reagents for B/Brisbane cell-derived and NIBSC has prepared

21 a reagent for reassortant BX-35 cell-derived. As far as

22 CBER's status of the antiserum is concerned, we have a lot

23 of antiserum available in our stock, and we are in process

24 of preparing additional lot of antiserum.   And this is all

25 in plans.

1   Again, the blue words are there to remember.

2   Coming to the influenza B for quadrivalent

3 formulation. As we all know, quadrivalent vaccines are

4 supposed to contain three strains that are recommended for

5 trivalent vaccine, with an additional B strain from

6 alternate B lineage, referred to as the second B strain.

7 For the 2016-2017 northern hemisphere season, WHO had

8 recommended that quadrivalent vaccine contain

9 B/Phuket/3073/2013-like virus from Yamagata lineage. Last

10 year wildtype B/Phuket and wildtype B/Utah, which is also a

11 B/Phuket-like virus, were used in vaccine production.

12   For egg-based product prepared using B/Phuket

13 virus, reagents were prepared by CBER, NIBSC, and TGA. For

14 cell-based product prepared using B/Utah strain, CBER and

15 NIBSC had prepared reagents. As we all know, for 2017-2018

16 WHO recommendation is that there be no change for the

17 second B strain for quadrivalent vaccine.

18   I'm not going to go over again the list of the

19 various candidate vaccine viruses, which are available for

20 both the egg-derived ones and cell culture-derived. Again,

21 this is the same strain which has been recommended for 2017

22 southern hemisphere season. Looking over the current

23 status and availability of the reagents, we have the

24 reagent at CBER available for wildtype B/Phuket. Reagents

25 for wildtype Phuket are also available from NIBSC, TGA, and

1 NIAID. Reagents for egg-derived B/Brisbane/9 are also

2 available from NIBSC. For cell-derived product, reagents

3 for wildtype B/Utah strain were prepared by CBER and they

4 are available. Similar reagents were prepared by NIBSC and

5 they are also available.

6   Currently CBER has three different lots of

7 antiserum available, so we are good on that.

8   So now, coming to some general comments. This is

9 mostly directed for the users of these reagents. Please

10 remember that only CBER-authorized reagents should be used

11 to test potency of vaccines marketed in the United States,

12 and we really request please consult with CBER before

13 starting to use any reagents. And as all of you know, CBER

14 collaborates with other ERLs in calibration of reagents,

15 and can authorize the use of those reagents.

16   When CBER authorizes the use of reagents from

17 other ERLs, it's expected that users have to obtain these

18 reagents directly from ERLs. CBER recommends the use of

19 reference antigen and reference antiserum from same source,

20 same source meaning from a particular ERL, as what colors

21 appear in their testing activity, and this will avoid a lot

22 of discrepancies.

23   We'd like to point out that the antisera lot may

24 need to be changed over time due to the limited amount

25 produced per lot, and I think which I say to every year,

1 please we recommend that the users of the reagents please

2 keep a small supply of your current lot, or first lot you

3 started using, so that you can help in bridging the

4 reagents in future.

5   And we strongly recommend that the same reagent -

6 - I mean, it is desirable to use the same set of reagents

7 for your monovalent testing, your trivalent and

8 quadrivalent formulation, and subsequent follow-up studies,

9 so this will avoid all of the discrepancy if you start

10 changing reagent sources in between.

11   There are products being made for an alternative

12 production platform and if there needs to be, CBER will

13 work with the manufacturers of alternative platforms,

14 vaccines, and try to work out the production of any

15 specific reagents needed, or to evaluate suitability of

16 egg- or cell-based reagents for alternative platforms.

17   Please do not, if I ask I you start using reagent

18 at the start of the season, if you feel there is any

19 problem with us please communicate with us sooner, so we'll

20 try to work it out what is going on.

21   And lastly, I would like to remind that for any

22 inquiries regarding CBER reference standards and reagents,

23 availability, and shipping, please contact CBER Standards

24 at the email address provided here.

1   In closing I want to emphasize that we at CBER

2 are committed to make every effort to assure that reagents

3 appropriate for all strains selected are made available in

4 a timely manner. We also believe that making an influenza

5 vaccine available in a timely manner is a responsibility

6 shared by all of us here, and we all work together as a

7 team to achieve this goal. We've been doing this year

8 after year, and that's what we expect that hopefully we

9 would have a good season this coming season, too.

10   Thank you all, and I can take any questions.

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

12   DR. MONTO: Since there aren't different reagents

13 required for something like the live-attenuated vaccine,

14 how do you make your decisions about what reassortants and

15 things like that, that are going to be approved for live-

16 attenuated vaccines? I'm thinking of the A/Bolivia

17 reassortants, which turned out not to be, to have good

18 growth potential, as well.

19   DR. JOSHI: I think I would like Dr. Weir can

20 comment about.

21   DR. WEIR: For live-attenuated vaccines, the

22 suggested or the manufacturer's choice of a reassortant is

23 actually sent to CDC and they do an antigenic analysis that

24 it's like the recommended strain, so that's very unique to

25 that particular manufacturer.

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

2   The next presentation will be comments from the

3   manufacturers by Dr. Beverly Taylor, the head of influenza

4   scientific affairs and pandemic readiness at Seqirus

5   Vaccines Limited, in the United Kingdom. Dr. Taylor?

6   **Agenda Item: Comment from Manufacturers**

7   DR. TAYLOR: Good morning, everybody. First of

8   all, I would like to thank the VRBPAC committee for giving

9   us the opportunity to give an industry presentation. So

10   thank you very much for that.

11   I'm going to start off with a diagram that you

12   have seen before just showing the timing of manufacturing

13   and how that relates to the strain decision timing. So you

14   can see here on the diagram that the strain selection by

15   WHO is usually late February, four strains now. We have

16   the quadrivalent vaccines, will be recommended, and the

17   strain selection is based on surveillance that is carried

18   out on an ongoing basis.

19   If you also look at the timeline, you can see

20   that in order to produce sufficient quantities of vaccine,

21   vaccine manufacturers have to start production at risk,

22   with at least one strain. Sometimes moving to two strains.

23   And obviously this is strain selection dates. If

24   they get later, the likelihood of having to move to a

25   second strain is increased. Once we have the selected

1   strains, sometimes if there is a strain change, we have to

2   produce new working seeds, which we can see here, and then

3   we are going to produce those strains and then we get to a

4   point in the campaign where we have the calibrated reagents

5   available. If there has been a strain change, we need to

6   wait for the new SRID reagents, and once we have the

7   information of how much of the three or four strains have

8   been produced, the last pass of the manufacturing campaign

9   is basically strain balancing. This is really important

10 for manufacturers, because we don't want to produce too

11 much of one strain and not enough of another, because that

12 will limit the number of the final vaccine doses that we

13 can produce.

14   Once we have the standardized reagents as well,

15 we can commence formulation. We can also commence our

16 stability studies on the vaccine and then move to filling

17 and packaging and distribution.

18   So this table just summarizes the timing of the

19 strain recommendations over the last 20 years, just

20 highlighting that since 2010 we have seen the strain

21 decisions at WHO and consequently the VRBPAC decision being

22 later and later, and this causes some challenges for

23 manufacturing, because the period that we manufacture at

24 risk is increasing with every week or even day of delay of

25 the strain decision.

1   So this is the same diagram that I showed again,

2   but I just want to show you the potential impact of a later

3   decision. So we can see here that if that decision moves

4   into March, all the other steps -- you know, some of the

5   previous speakers have talked about how everything is

6   interrelated. So if we have a later strain decision, if

7   there is a strain change, we're later in supplying antigen

8   for reagents, the calibrated reagents are available later,

9   we start formulating later, and we haven't as yet seen an

10   impact on the start of vaccination dates, but I guess the

11   very clear message from manufacturers is if you keep

12   squashing that manufacturing window then there will reach a

13   point if the strain decision becomes so late that we are

14   concerned that we will start to see an impact on vaccine

15   supply timings.

16   So the graph on the left-hand side here just

17   shows the total number of doses distributed in the United

18   States over approximately the last 20-something years. You

19   can see that over the years, the number of doses

20   distributed has increased significantly, and if you look at

21   the right-hand graph you can see the distribution of doses

22   throughout the 2015-2016 season. So you see the

23   vaccination starting in September and really peaking and

24   you see that tailing off around the end of November.

1   Obviously, to ensure vaccine supply, we're trying

2   to balance a number of different factors here. So we

3   obviously want well-matched strains. There has been a lot

4   of discussion around that today, and that's obviously a key

5   component. But we also need to have sufficient quantities,

6   and in the timeframe that is expected, too.

7   And just to comment that the number of doses

8   distributed in the United States so far for this current

9   season is just under 146 million doses.

10   So I mentioned before that manufacturers have a

11 number of concerns about the later strain recommendations.

12 Obviously one I've just mentioned is that manufacturers

13 carry out a larger proportion of their manufacturing

14 campaign at risk. This year that's around two months. As

15 many manufacturers have to start manufacturing in January.

16 If the strains manufactured at risk are not recommended and

17 if manufacturers have moved to a second strain manufactured

18 at risk, that risk increases.

19   Then the only -- it's not only an impact on the

20 manufacturer to discard those batches, but also we never

21 recover those manufacturing slots. So if we have

22 manufactured the wrong strain at risk, then we have

23 potential resource limitations and we will be trying to

24 catch up for the rest of the campaign, which could again

1 impact the timing and the quantity of the vaccine

2 available.

3   The other additional pressure, as you saw in the

4 previous graph, the number of doses distributed in the

5 United States has increased significantly. So that means

6 that that is even more pressure. So we are not talking

7 about a lower number of doses here. We are showing an

8 increase in the number of doses being distributed, and if

9 there is a later strain recommendation, that manufacturing

10 window being more and more challenged, and we feel that all

11 these different components added together are significantly

12 increasing the risk of delaying the vaccine available.

13   Obviously for this year for WHO, they did not

14 change the strains from the southern hemisphere. So maybe

15 we would not see something in this particular season, but

16 for future seasons, if there were to be strain changes,

17 this could have an impact.

18   So we have had many discussions. HHS BARDA held

19 some mismatch meetings in 2015, and out of that they have

20 developed their seasonal influenza improvement initiative,

21 and there are many suggested improvements to have

22 representative virus or CVVs identified early. Really push

23 for high growth reassortants and perspective -- the

24 perspective yields known ahead of time. This includes non-

25 frontrunner viruses. So if we were to see, you know, we

1 can see for some of the strains of virus that it's quite a

2 complex genetic picture.

3   So something that seems like a non-frontrunner

4 virus, that could change very quickly. So if we also had

5 CVVs for those we would be able to respond much more

6 quickly. Also preparing more antigens and critical

7 reagents for more of the candidate vaccine viruses at risk

8 so that we have those earlier.

9   However, I think the key message here is there

10 has been a lot of discussion about this. There's a lot of

11 good work planned, but we are not there yet, and these

12 improvements really need to be in place if we are going to

13 see the benefits of them.

14   So what do manufacturers do to prepare as much as

15 possible for the influenza campaigns and particularly

16 around the northern hemisphere 2017-2018 season. So we

17 track surveillance data through summaries of internal WHO

18 TCs that are held to look at the surveillance data, and

19 they now include a table at the end of that summary, which

20 lists out all the viruses of interest. So that gives

21 manufacturers an idea if there is a new area of interest or

22 there's a particular virus that is of increasing interest.

23   We use websites such as the WHO FluNet and CDC

24 FluView to look at the surveillance. Again, we do the best

25 that we can with the data, but it's not always a clear

1 picture. You know, if you look at the B strains this year,

2 you can see the B/Victoria overall over a period of time is

3 higher, but some weeks it seems to be B/Yamagata higher.

4 So it is really not always clear.

5   We also track the availability of candidate

6 vaccine viruses for manufacturing through the WHO chaired

7 technical TCs, which are held every two weeks, and for this

8 year the ones that we started for the southern hemisphere,

9 we actually continued right up to the northern hemisphere

10 strain recommendation to give us more information on

11 surveillance for the northern hemisphere.

12   And also we now have a spreadsheet of viruses of

13 interest and what stage of preparation they are at. This

14 is really for the high growth reassortants. This

15 spreadsheet was developed between NIBSC and the Crick

16 Institute in the UK. It's really in its infancy. We have

17 only started using it in the last few weeks, but the idea

18 is that this will provide timely updates on the development

19 status for the new strains that will be available for

20 manufacturing, and ultimately we hope to get that as a

21 real-time tool that we could log into at any time and see

22 what the status is.

23   And industry also closely engages with the WHO

24 and U.S. agencies at multiple forums. If you just look at

25 the -- so the line in the middle is sort of the calendar

1 running from one VRBPAC meeting to the other. Here, if you

2 look at the lighter blue squares, there are some really key

3 dates in our calendar where we get detailed surveillance

4 information. So if you look here, we have an NIBSC meeting

5 in July. We have a BIO-FDA Flu Review in December, and we

6 have another NIBSC flu review usually held either late

7 January or early February, and they're key opportunities

8 for us to really understand the surveillance and what

9 candidate strains are available and where reagents erupt

10 to. So they are really key meetings for us.

11   We also have a host of other meetings that we are

12 involved in, and we have industry representatives

13 attending. So we do work very closely and collaboratively

14 to resolve issues, to get updated information. We are

15 working together to improve influenza vaccine supply,

16 pandemic preparedness, and I hope that this slide really

17 illustrates how closely that we're working with the

18 agencies.

19   So this slide is just giving an overview of some

20 of the strains which have been evaluated for the upcoming

21 northern hemisphere season. So based on the WHO

22 recommendations made last week, these -- so the WHO

23 recommended like strains are in red on the slide, and the

24 candidate viruses are listed underneath. So these are what

25 manufacturers have been evaluating for the upcoming season.

1   So that concludes my talk about the preparations

2   for the upcoming season. I just want to switch gears a

3   little bit and mention the Nagoya Protocol. Again this was

4   raised last year during the industry presentation, and it's

5   something that we continue to be extremely concerned about.

6   So just a brief reminder. The Nagoya Protocol was

7   developed from access and benefit sharing discussions at

8   the Convention on Biodiversity, which was adopted in 2010.

9   It came into force in October 2014, when the 50th company

10   ratified the Nagoya Protocol.

11   So the objectives are to ensure access to genetic

12   resources and related traditional knowledge for potential

13   use and ensure that users and providers of the genetic

14   resources and related traditional knowledge agree on fair

15   and equitable sharing of benefits arising from their use.

16   It is important to point out that this came through the

17   agricultural routes, the environmental routes, rather than

18   the public health routes, but it obviously covers viruses.

19   Many countries are including pathogens in the legislation

20   that they are developing around Nagoya, and we are

21   concerned that this will cause delays in supply viruses for

22   a seasonal vaccine manufacturing.

23   So there have been some key developments this

24   year. So WHO carried out a review in 2016 to look at the

25   potential impacts on public health of the Nagoya Protocol,

1 and the WHO and the CBD are being encouraged to identify

2 and develop means to mitigate the potential impact of

3 Nagoya obligations on the sharing of influenza strains,

4 because under Nagoya companies would have to negotiate

5 bilateral agreements with the supplying country, which

6 could cause significant delays and we have previously

7 estimated that this could be up to three months delay in

8 receiving or having the ability to move forward and work

9 with the strains.

10   Industry does support escalating both the WHO

11 GISRS system as well as the PIC framework to something

12 called specialized international instruments for access and

13 benefits sharing. What this would do would be if they were

14 recognized under the Nagoya Protocol, then both seasonal

15 and pandemic influenza viruses would become exempt from

16 time-constraining Nagoya obligations in the future. We

17 heard from WHO last week that there is a meeting in

18 Montreal, the third week in March, where they will be

19 working with the CBD secretariat to develop a process

20 through which to identify specialized international

21 instruments. So that is like the first step forward,

22 because currently there isn't even a process under Nagoya

23 to recognize these specialized instruments.

24   The United States is not a signatory to Nagoya.

25 However, we are not sure of the potential impact on

1 influenza vaccine availability in the United States,

2 because there could still be some restrictions through the

3 Nagoya Protocol.

4   Just to make the point, the next slide shows from

5 the previous slide when I listed out all the candidate

6 vaccine viruses being considered for the upcoming season, I

7 have crossed out all the vaccines that come from Nagoya

8 signatory countries. Scotland is still on there. The UK

9 is a signatory but has waived their right to benefits

10 through Nagoya. So that remains on the list.

11   And this is the potential impact. It depends on

12 the local legislation and whether pathogens have been

13 covered by the local legislation in those countries, but I

14 just think that this slide is quite powerful in showing the

15 potential impact that we would have, because it could

16 vastly reduce our choice of viruses, which could reduce our

17 ability to find a well-matched virus for the seasonal

18 influenza vaccine.

19   So in conclusion, the timing of strain selection

20 and vaccine supply requires close collaboration between

21 multiple stakeholders to ensure sufficient provision of

22 vaccine each season. This season we are as manufacturers

23 going through our preparedness -- our preparedness is

24 ongoing. However, we identified future improvements that

25 could help us respond more quickly and react more quickly

1 to changes and maybe mitigate later strain recommendations,

2 but I think it's very clear from our point of view any

3 delay in the strain recommendation would potentially cause

4 a delay in vaccine supply.

5   And then the final point is that adherence to the

6 Nagoya Protocol could result in delay in influenza vaccine

7 supply. We know that WHO and CBD are collaborating to

8 identify ways of mitigating this, but it still remains a

9 significant concern for manufacturers.

10   Thank you very much for your attention.

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

12   DR. SCOTT: I have a question on how do you choose

13 the strains that you do at risk before -- is it across the

14 same across all the companies, or does each company just

15 choose one strain or two strains that they do at risk?

16   DR. TAYLOR: I think usually based on the

17 surveillance, there is usually one virus that is -- you can

18 never say it's never going to change, because in 2008 we

19 had three strain changes, but it's least likely to change,

20 and I think that the majority of manufacturers would choose

21 that strain. So for example, for this year, the H1N1 pdm09

22 virus was probably the least likely to change. It was very

23 unclear with the H3N2s. For the quadrivalents, the Bs were

24 clear, because the Bs for each lineage, the strains weren't

1 changing, but for manufacturers still producing TIV, which

2 B was going to predominate really has not been clear.

3   So I think the majority of manufacturers may have

4 chosen H1N1 this year. There's usually a clear frontrunner

5 for the strain to run at risk. Where we come into

6 difficulties, if the strain decision is delayed,

7 manufacturers may have produced enough of that strain and

8 have to switch to a second strain which is not so clear,

9 and that would increase the risk.

10   DR. BENNINK: From your slides, is all of the

11 manufacturing done by September or something like that for

12 the current season?

13   DR. TAYLOR: I would say for the majority of -- I

14 can't speak for every manufacturer, but I would say the

15 majority of manufacturers, all manufacturing is completed

16 by September. There may be still some filling in,

17 packaging activities, ongoing.

18   DR. EDWARDS: Thank you very much. We are running

19 a trifle behind. So I think we will have 45 minutes for

20 lunch. We can come back at 1 o'clock and if you want to --

21 if you need longer than that to complete your meal, you can

22 bring it back here, but we will start at 1 o'clock. Thank

23 you.

24   (Lunch recess.)

25

1   **Afternoon Session**

2   **Agenda Item: Open Public Hearing**

3   DR. EDWARDS: For public hearing, are there any

4   individuals who would like to speak?

5   (No response.)

6   **Agenda Item: Committee Discussion, Voting, and**

7   **Recommendations**

8   DR. EDWARDS: If not, then I think we can get to

9   our committee discussion, voting, and recommendations.

10   Do we want to put up the voting questions, or do

11   we all have them? We could do that. Could we do that?

12   Just put the voting questions up on the slide?

13   Okay, I'd like to open the discussion for

14   concerns and discussion around the first question, the

15   composition of the trivalent vaccine, thoughts, concerns,

16   committee?

17   DR. WHARTON: Thank you. My understanding from

18   the presentations is that it appears that the situation in

19   North America for Yamagata versus Victoria may have been a

20   little different than for other parts of the northern

21   hemisphere, and I wondered if Jackie or Lisa could confirm

22   if that's correct.

23   DR. KATZ: So based on the data we had available

24   for the vaccine consultation meeting last week, both Europe

25   and North America were seeing slightly, like 54, 56 percent

1 B/Yamagata, and 46, mid-40s percent of B/Victoria, but it

2 was pretty close.

3   For Central, South America, and obviously there's

4 less data from them also, and Asia and Africa, they

5 definitely saw more B/Victoria in the period we were

6 looking at. Oceania, which is largely a lot of Australian

7 data, they had quite a swing to B/Yamagata in this season.

8   DR. EDWARDS: The B that is currently circulating

9 sort of in the tail of the strains this year then would be

10 about equally distributed between the two strains in the

11 United States, or do you have enough data to say?

12   DR. KATZ: It's probably changing week by week and

13 certainly I think as there's been an upswing in Bs, there

14 is a little bit more B/Yamagata.

15   The data that I'd put into this table, to the pie

16 charts that I showed you, is our most recent data. So you

17 can just see that month by month, it sort of is cycling up

18 and down, but currently in the United States, yes, I would

19 say B/Yamagata is edging out B/Victoria.

20   DR. WHARTON: Well, of course this is exactly the

21 reason why this committee, several years ago, started

22 talking about the benefits of including both B strains and

23 annual influenza vaccination, which we are doing to an

24 increasing degree in the United States, but we do still

25 market trivalent influenza vaccines -- we still do market

1 and use trivalent influenza vaccines in the United States

2 and I'm very conscious of influenza vaccination being a

3 global enterprise where companies manufacture vaccines for

4 use in multiple countries.

5   I hate asking this question, but I'm going to ask

6 it. If we were to select a B strain that differed from the

7 WHO recommendation, would that adversely impact vaccine

8 production for the U.S. market? I'm not sure who this

9 question is directed to.

10   DR. EDWARDS: Perhaps Dr. Greenberg?

11   DR. GREENBERG: I don't have a direct answer to

12 the question, primarily because I don't know what each of

13 the manufacturers have done with regard to the strain or

14 strains they're producing at risk because I'm speculating a

15 bit, but of course my colleagues in the audience can be

16 specific. But if, for example, a manufacturer is not

17 manufacturing one of these strains right now, then I'm not

18 sure that it would make any difference, but I'm sorry; I

19 don't have a direct answer.

20   DR. WEIR: Just to follow up on that, this is

21 really sort of a question for the manufacturers obviously,

22 but it seems like one impact could be for manufacturers who

23 are making vaccines worldwide, and if the formulation of a

24 trivalent is different for the United States versus

25 somewhere else, and I don't know how many companies that

1 would affect. I mean, you'd have to almost poll individual

2 companies and find out.

3   DR. EDWARDS: The high dose influenza vaccine,

4 that's still a trivalent, correct? Is that planned to be a

5 quadrivalent?

6   DR. GREENBERG: Do you want me to answer that as

7 the industry representative, despite the fact that I know -

8 - it's a little bit out of turn or place, but I'll answer.

9 It is a trivalent and there are clinical trials taking

10 place to move that to a quadrivalent.

11   DR. JANES: Dr. Katz, you mentioned the modeling

12 work predicting the future circulating strains and the

13 difficulty of doing that, but can you make any comment on

14 what those projections have done to inform the WHO

15 recommendations and how it relates to the Yamagata versus

16 Victoria?

17   DR. KATZ: No, in fact, one group just only really

18 addresses the H3N2s since that's our most problematic one.

19 The focus really is within a lineage for the Bs, which, is

20 there is genetic diversity, what is likely to take off? So

21 I can look back on the package, but I don't recall they

22 made predictions about which lineage would take over.

23   As we've said, it varies by region in the world,

24 and it's quite dynamic and different. It's going up and

25 down all the time with respect to the proportions of B.

1   DR. MONTO: The group at Cambridge, and I think

2   that their approaches have been published, have suggested a

3   variety of approaches such as just alternating the strains

4   and trying to anticipate which way things are going.

5   Given the fact that the whole world is not going

6   to quadrivalent vaccine, is it time to revisit those

7   issues? Because it seems like one of the reasons we want

8   to quadrivalent was because of the inability to predict,

9   and that inability to predict is still present.

10   DR. MCINNES: So we've discussed this for years.

11   It's had a Yamagata year followed by a Victoria year

12   followed by a Yamagata year, right? So I had a question.

13   Given that we're concerned about infants and children which

14   regard to B, are there any data about what U.S. children

15   are getting with regard to trivalent versus quadrivalent?

16   DR. WHARTON: Well, I think we can identify what

17   we buy for the public-sector program, which, off the top of

18   my head, I don't know.

19   DR. GREENBERG: I don't have much to add, just to

20   say that it is difficult to track because for the most

21   part, influenza vaccines are not age-specific, so then

22   therefore it's difficult to track which of the vaccines get

23   into children of most ages. There are of course some

24   exceptions to that, but for the most part, it's hard to

25   know which vaccine gets to which age group.

1   DR. EDWARDS: Any comments or perhaps, Patrick, do

2   you want to bring up your H3N2 concerns again, so we can

3   ponder those again?

4   DR. MOORE: I am concerned. Well, I think that I

5   am not convinced that the Hong Kong strain is going to be

6   any better next year, but unfortunately I don't see any

7   evidence that there is another strain that is better than

8   Hong Kong.

9   Also, the other thing I would reiterate is that

10   the data looks very interesting in terms of whether there

11   is a cell-based versus egg-based difference in antigenicity

12   for the vaccine based on the ferret data. Whether that

13   pans out I guess we'll know, but certainly we should be

14   very focused on finding out whether there is a cell-based

15   vaccine efficacy that's different from the egg-based

16   vaccine efficacy for the H3 strains in the upcoming year.

17   DR. MONTO: The problem is, how do we find this

18   out? With the vaccine effectiveness studies, which are the

19   only ways we can find out on an annual basis what's going

20   on, the problem is that not enough of the cell culture-

21   based vaccines being used in the United States to be able

22   to say that it's better, and there's no likelihood that

23   this is going to change. Again, we need more evidence for

24   exactly what's going on based on what we know. We think

1 that the egg adaptation is one of our many problems with

2 the H3N2 vaccines.

3   DR. MOORE: Is there any evidence for another

4 candidate strain that would be better than Hong Kong,

5 particularly a 3C.2a1 strain that would be more closely

6 related to the centroid of the genetics of the new viruses

7 that are coming out?

8   DR. KATZ: So the analysis that the collaborating

9 centers did include some more recent viruses. Of course,

10 the question is there's 3C.2a1 viruses of which we have

11 many that are grown in cell culture that are being

12 characterized, but few of them have been isolated in eggs

13 exclusively because that's another challenge, that 3C.2a1

14 viruses are being a little more difficult to isolate in

15 eggs.

16   But we had one candidate at CDC that's very poor,

17 and the other two are just unknowns at this time. They're

18 not at the stage where we could hand them over to

19 manufacturers and that's not likely to be -- they're still

20 in development as candidate vaccine viruses as far as I'm

21 aware at different laboratories, and then it would take

22 quite some time to do characterization and really evaluate

23 how well they're reacting compared with circulating

24 viruses.

1   I mean, the antigenic studies we've done says

2   that the 3C.2a1's, although genetically they're different,

3   that antigenically, 3C.2a1 Hong Kong/4801 covers those

4   viruses quite well, and we don't have a good 3C.2a1

5   candidate that has been evaluated to any extent.

6   DR. BENNINK: Another one that is not very

7   broadly, probably, as used as the protein science is the

8   recombinant version of theirs. Is that being tracked in

9   efficacy at all as separate from the others?

10   DR. MONTO: It is the same problem. If not enough

11   is used, you don't have a sufficient sample size. We do

12   have this year, probably, results which might be useful for

13   the high dose, but that's only because a lot of high dose

14   is currently being used in that age group.

15   DR. EDWARDS: Certainly those are important

16   questions, whether those could be generated into funding

17   opportunities to address those questions or to specifically

18   add vaccines into your study. I don't know whether that's

19   an option either.

20   DR. MONTO: I think there are options to enrich

21   the use of certain vaccines in certain population groups.

22   I think it just takes planning and attention.

23   DR. EDWARDS: It seems like that the H3N2 we've

24   sort of addressed and I think we, perhaps, I truncated the

25   B discussion a little bit too quickly. Hana, you had

1   brought this up originally, do you have some thoughts about

2   one B as opposed to another B, to be or not to be?

3   DR. EL SAHLY: Ideally, I would think two B, but

4   if the pattern of 50/50 is going to continue, or 40/60, to

5   me, the difference doesn't seem that big, and I don't know

6   how this suggestion would impact delivery of vaccine,

7   manufacturing of vaccine, which are at times more important

8   considerations alternating seasons, but the impact on

9   public health in terms of delivery and manufacturing would

10 also have to be considered.

11   DR. EDWARDS: Any comments on H1N1? Are we ready

12 to vote or do we have some other comments? Go ahead,

13 Patrick.

14   DR. MOORE: This is not a strain-specific comment,

15 but it is based on the presentation this morning with the

16 vaccine timeline. Can I make a comment or do you want me

17 to do it later?

18   So the industry representative made a valid point

19 this morning, that the supply timeline is very problematic

20 with late VRBPAC and WHO meeting dates and how to resolve

21 that because we really need -- there's a pressure to move

22 the dates to later, as late as we can get them so that we

23 can get more surveillance data which is critical for us

24 making a good decision, whereas having that decision

1 earlier is good for industry to be able to make the

2 vaccine. Both of them are important things.

3   One possibility, and I just raise this, is that

4 it may be valuable for FDA to start discussions with CDC

5 and WHO in order to try and resolve this, to try and push

6 the VRBPAC dates to an earlier date, perhaps late February.

7   Or alternatively, one suggestion would be to

8 reserve for the committee two separate dates, one in, say,

9 early- to mid-February, and one early March, and have CDC

10 be able to tell us which, if there is a new strain that's

11 emerging in January and February that obviously might

12 impact the strain decisions, they could tell us which date

13 they need to have surveillance data accumulate by the time

14 they could present. It's just an idea for trying to

15 resolve this practical problem.

16   DR. MONTO: I remember a few years ago when the

17 VRBPAC met before, because of logistic considerations,

18 before the WHO's strain selection meeting, and it was

19 futile as they say because you couldn't really do anything.

20   DR. MOORE: Can we or can someone, meaning FDA,

21 CDC, approach WHO to try and move back their date or at

22 least try and coordinate it?

23   DR. KATZ: Yeah, after we had discussion with

24 industry, WHO is aware. They will consider, so the global

25 influenza program at WHO sets those dates, and there are

1 multiple factors that play into it, but I think as we

2 discussed with industry last Thursday, there is the desire

3 to keep it maybe not as late as it was this year, but which

4 was, I'm not sure why, but I think it was just the way the

5 calendar fell.

6   But recognizing that we don't want to be pushing

7 this into March, but we still are most likely not going to

8 move it back to where it was 10 years ago where it was sort

9 of more consistently mid-February. We need some middle

10 ground there to really get the best and most data we can

11 for the decision-making process. So we heard industry loud

12 and clear, and it will be up to the global influenza

13 program to make that decision for next year.

14   DR. JANES: Back on the B lineage question, is

15 what I am hearing correct that that the main consideration

16 not to consider swapping out the B in the trivalent vaccine

17 is manufacturing considerations, or are there scientific

18 reasons not to do that that I haven't heard?

19   DR. KATZ: I guess at least this year, it looks

20 like about 70 percent of the influenza B/Victoria

21 infections are in persons under the age of 25. So it's

22 affecting children more heavily. So if children, some

23 children, are only getting TIV, maybe that's a rationale

24 for keeping B/Victoria.

1   I think when WHO has alternated, I mean, they

2   were on a cycle maybe about seven or eight years ago where

3   they were alternating and it seemed like they just kept

4   missing it. They were like, one season behind, and I don't

5   know, we really can't predict what's going to happen except

6   the current circulation of Bs worldwide suggest that both

7   of them are quite comfortable, both lineages are both

8   circulating quite comfortably, and one isn't sort of

9   competing out the other at this time. Certainly that seems

10   to be, and everything was at a low level.

11   The other thing to realize is I don't think we've

12   had an exclusively B season for a long time. B's always a

13   part of the strains that circulate and may not even be the

14   dominant one as we've seen with H3s and H1s dominating in

15   recent years.

16   DR. MCINNES: Somewhat lighthearted, but I am

17   reminded of the great Rob Webster. He used to stand and

18   say, if only I had a crystal ball. So it's that situation,

19   right?

20   DR. KOTLOFF: I just want to clarify again how

21   global our recommendation is supposed to be. If I'm

22   looking at the right data, I mean, we're talking about 75

23   to 80 percent of the Bs in Africa and Asia, which are much

24   more populous than Europe and America, although I don't

25   know what the number of vaccines given is like, or

1 Victoria, whereas we're talking of very close, it's like

2 40/60 in the opposite direction in Europe and North

3 America. So should our perspective be the number of people

4 worldwide, the number of vaccines that are administered

5 worldwide, or just the United States? What are we

6 answering for?

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

8 jurisdiction?

9   DR. WEIR: No, not really. This is not a new

10 problem in some ways. The committee is clearly supposed to

11 make recommendations for the United States. How you weigh

12 all of the data worldwide is the problem, and you're trying

13 to predict are strains that are circulating in one region

14 like Africa going to be the ones that circulate more next

15 year, or the ones in some other part of the world? I don't

16 have an answer for that.

17   DR. MONTO: I will say something which I was not

18 planning to say, and that is, what would the consequences

19 be if we made a decision, given the fact that influenza

20 vaccine is a global commodity, that was not in agreement

21 with the recommendations of the WHO? How would the

22 manufacturers, David, respond to something like that from a

23 practical standpoint?

24   DR. GREENBERG: Well, I think that these sorts of

25 questions do have to go to the individual manufacturers as

1   to whether or not there's going to be any impact on which B

2   lineage goes into the trivalent and quadrivalent vaccines

3   and what impact that would have on manufacturing and

4   supply. I think that in the end, obviously, the vote of

5   this committee then is how CBER licenses each

6   manufacturer's vaccine.

7   So when you ask, would it matter in terms of the

8   recommendation to WHO, from a manufacturer's standpoint,

9   it's kind of agnostic because whatever you all decide is

10 what the manufacturers must do. But I can't answer the

11 question. If you want more detail about what a decision

12 opposite of WHO would have on the manufacturer's process

13 and the supply and timing, I think each one needs to be

14 asked.

15   DR. WEIR: Just to clarify, this is not a

16 regulatory question. I mean, manufacturers would just

17 follow the recommendation and submit the same supplements

18 they always do. So if there's a question here, it's really

19 for manufacturers.

20   DR. BENNINK: Jackie, do you know, you gave us a

21 percentage under 25 of 70 percent or something like this,

22 do you know what the over 65 is, since that's a trivalent?

23   DR. KATZ: Well, not all the over 65s are getting

24 high dose. They could get standard which could be QIV.

25 I'm just looking at, if I can find it again, this is just

1 reading off our week 8 FluView, and it looks like in the 65

2 and older age group, so for those infected with B/Victoria

3 lineage, it's a small proportion of those over 65, it looks

4 like it's sort of less than 10 percent.

5   So the older age group isn't really getting that

6 affected by B/Victoria this season. It's more like 25

7 percent for the B/Yamagata lineage. The B/Yamagata lineage

8 is sort of more like, the age distribution is a little more

9 like the influenza A distribution. Did you have that? You

10 had on your slide, didn't you, Lisa, this age breakdown?

11 Oh, you didn't present that.

12   So it looks like in the older age group for this

13 season in the United States, that they're not heavily

14 affected with B/Victoria, and if they got B, I guess

15 there's a greater proportion of that age group that had

16 B/Yamagata.

17   This is, again, only where we have that lineage

18 breakdown, because there's some Bs that we don't have

19 lineage determined for.

20   DR. JANES: There would be some protection for

21 individuals who were previously vaccinated with the

22 B/Victoria lineage and my question is what do we know about

23 the durability of those immune responses and what those

24 would predict about their protection this year if they were

25 vaccinated with a different B?

1   DR. EDWARDS: The granularity of your VE data, in

2   terms of the B, can you comment on that, Lisa, on how

3   effective the trivalent vaccine was for the B strains?

4   DR. GROHSKOPF: Not specifically for the trivalent

5   because those data weren't broken down by the trivalent and

6   quadrivalent, the B figure that was presented as overall

7   and actually was not even broken out by age. Was that the

8   question, whether the trivalent --

9   DR. KATZ: Right, but overall, or for B/Yamagata

10   specifically, it was like 70-ish percent.

11   DR. GROHSKOPF: Right, 70-ish percent, and even

12   though those weren't broken down by lineage, again, only 1

13   percent of the total isolates were for the B data thus far

14   were Victoria. So essentially that's a figure for

15   Yamagata.

16   DR. KATZ: That's in those sites, they had more

17   B/Yamagata than B/Victoria.

18   DR. JANES: But understanding that the VE data are

19   sparse and just looking at immune responses that these

20   vaccines generate, how durable are those?

21   DR. GROHSKOPF: In terms of immunogenicity data,

22   if we're speaking of durability of immune response, my

23   understanding of that literature is most of it examines

24   durability for flu A, and there's a lot of discussion and a

1 good number of papers for the last few years for waning of

2 immunity, particularly in the older population.

3   When waning is observed, it's mostly been

4 observed for H3, but I don't think there has been, and

5 there are probably some people here who may know more about

6 this than I do, most of what's been observed is in the H3,

7 not so much the H1, but I don't think the literature

8 database is as rich for B as far as durability of response

9 from season to season particularly in older people.

10   DR. MONTO: Yeah, the problem with B serology, the

11 fact that if you don't use either split antigens, you see

12 lower responses by far to B in the HI test has led us down

13 the garden path to think that our B vaccines weren't

14 working.

15   With this 1 to 40 magic amount that was supposed

16 correlate with protection, we still have the same problem.

17 One of the revelations from the vaccinate effectiveness

18 study is that the B study has consistently outperformed the

19 A(H3N2) vaccine, and we have less to worry about. Not only

20 that we have some evidence at least in adults that there's

21 cross-protection between the lineages. So it's really, our

22 big issue is H3N2 right now.

23   DR. WEIR: Can I follow up with what Arnold just

24 said? Does that mean you would place somewhat greater

1 weight on what might happen with children for the selection

2 of the B strain?

3   DR. MONTO: The problem again is we've had

4 relatively small numbers so we can't even say what a cutoff

5 would be in young children. Certainly from studies that

6 were done years ago where they were trying to give the two

7 doses, one in the spring and one in the fall, it looks like

8 it makes a difference with young children in terms of the

9 lineage, but whereas, and these are very young children who

10 are getting initial vaccinations. I think the history of

11 infection also falls in there and that's the thing that,

12 without longitudinal studies, you can never figure out.

13   DR. KOTLOFF: I needed some clarification. I was

14 just wondering, if you're looking at severity of disease,

15 if there is a greater representation of either of the B

16 strains. So I was wondering if there were any data on

17 deaths and then I went back to this slide in Lisa's talk,

18 the second slide that looks at hospitalizations, but the

19 key is missing, at least on what I have here, to know which

20 -- I think the green colors are the Bs but I can't tell

21 which is Yamagata and which is Victoria.

22   DR. KATZ: They are the green. Do you know which

23 is the lighter green?

1   DR. GROHSKOPF: I believe the darker green at the

2   base is the Yamagata, but I will check that and confirm it

3   right now, actually, because I think I can do that.

4   DR. KATZ: So the very dark green, which is at the

5   top of the green bars, is the Yamagata. Oh, hang on, no,

6   sorry, the darkest green is B lineage not performed. The

7   next one down, which is sort of the brightest, palest

8   green, is B/Victoria, and the bottom one, which is that

9   intermediate green, is the B/Yamagata. So that's showing

10   in recent weeks there's more B/Yamagata than B/Victoria.

11   DR. KOTLOFF: Do you know anything about the

12   deaths?

13   DR. KATZ: I think, Lisa, do you want to talk

14   about how we don't have subtyping on the virus information

15   on the deaths?

16   DR. GROHSKOPF: We don't have, at least pediatric

17   deaths, we don't have subtyping or AB information on all of

18   the deaths. For the current season deaths, it's reported

19   in the most recent review that there were two H3N2s, one

20   H1N1, two unsubtyped and one B, but we're dealing with a

21   relatively small sample size of one week there.

22   DR. KATZ: But each week it's been distributed,

23   sort of H3, B, there's no predominance that the pediatric

24   deaths are attributable to B, I would say.

1   DR. MONTO: Isn't there also a problem about

2   regionality with any of these? We're legislating for a

3   very large country, and there's going to be variation in

4   one region over another, especially with these. It can be

5   very different.

6   DR. GROHSKOPF: Correct, and again, I had

7   mentioned in the summary to the surveillance presentation

8   that in recent weeks, it appears nationally things are

9   starting to level off in terms of activity, but if you were

10 to look at different regions, it's not the same across all

11 regions. There's some where it may still be increasing,

12 some where it may be starting to plateau and decrease. So

13 we do have to, that's an excellent point, we have to keep

14 in mind that things aren't going to be the same in every

15 region in the country. The predominant viruses won't be

16 the same in every region of the country necessarily. So

17 that's an important point.

18   DR. GREENBERG: I just thought I'd add a comment

19 since there's a lot of focus on B and children, and I

20 commented earlier that you don't always know which of the

21 vaccines get into each age group.

22   But I will say that, and I think I'm speaking

23 correctly here, if I'm wrong, someone corrects me, that's

24 fine, but I think in general, a few years ago when

25 quadrivalent vaccines began to come onto the market from

1 the various manufacturers, for the most part, pediatricians

2 thought that that was the right thing to do. The children

3 were probably going to be more susceptible to one lineage

4 versus another if it wasn't in that trivalent vaccine

5 during that season, and really they accepted the logic.

6   Although I don't know exactly what percentage of

7 children received quadrivalent versus trivalent, there are

8 still trivalent vaccines that are on the market, so some

9 do. But I think that in general, most children receive

10 quadrivalent because most pediatricians have accepted that

11 as the proper vaccine to give in that age group.

12   DR. EDWARDS: I think also prior to that time,

13 there were some papers that looked at predictions, not

14 quite exactly what Jackie was saying with WHO and trying to

15 predict, and by and large, it was like flipping a coin in

16 terms of predicting. So I think that was clearly the case.

17 So it was problematic.

18   DR. KOTLOFF: Is there any mechanism or way to get

19 the message out, particularly for children, that

20 quadrivalent would probably be a better bet because of

21 their Victoria distribution?

22   DR. EDWARDS: I think certainly that's what the

23 COID from the AAP tries to do, and so I think that has been

24 a message that's consistently been preached by the

25 pediatricians and certainly is a reasonable one.

1   Okay, why don't we go around and then make any

2   last comments before we vote? Let's start with Pam. Are

3   there any things that you would like to bring up before we

4   vote or any thoughts that you wanted to share?

5   DR. MCINNES: I'm pleased to hear about the

6   pediatricians, because that was what my question, I was

7   trying to get at what percentage we think kids are getting,

8   given that that's the population I'm concerned about with

9   regards to this conversation in B. So that was helpful.

10 Thank you. No, nothing else.

11   DR. WHARTON: I guess several years ago we

12 realized we were not able to predict what was going to

13 happen with these strains and so it is, cognizant to the

14 fact that what I'm about to say is probably wrong, that if

15 we were to make a decision about a B strain, only based on

16 U.S. surveillance data and without considering anything

17 else, I would personally advocate for considering making a

18 change to the Yamagata lineage.

19   But that is not the case. The case is we are in

20 a country that uses vaccines manufactured by multiple

21 global companies, and I'm concerned that a change would

22 adversely impact the availability of vaccine in the United

23 States, and given that so much quadrivalent vaccine is

24 already being used, and a lot of that, I don't know how

1 much, in children, it does seem like the risks of making

2 that change may very well exceed the benefits.

3   DR. GREENBERG: I didn't have a comment, but from

4 Melinda's comment, I'd like to just acknowledge that it

5 didn't actually click with me until you just said that that

6 absolutely, and so as representing industry, I think what

7 you said makes a lot of sense because there are -- and

8 again, I invite people from industry from the audience to

9 comment further, but you're right. There are manufacturers

10 that make vaccines in either a single or limited number of

11 manufacturing sites, and their vaccines are distributed

12 globally.

13   So to the extent that this committee's

14 recommendation might be different than WHO, you're right,

15 that could have major impact.

16   DR. EDWARDS: That would be a confusing message as

17 well, exactly. All right, I think then we are ready to

18 vote. The first question is for the composition of the

19 trivalent 2017.

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

21   DR. EDWARDS: Yes, please. So the composition of

22 the trivalent 2017-2018 influenza virus vaccine in the

23 United States, does the committee recommend the inclusion

24 of A/Michigan H1N1-like vaccine? Yes or no?

1   DR. ATREYA: Before you vote, there are three

2   buttons on the voting machine, the microphone, and so this

3   voting should be simultaneous and after you vote, then the

4   results will be computed and then will be projected and

5   then I will have to read them aloud for the public record.

6   Thank you.

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

8   Vote.

9   DR. ATREYA: Dr. Scott said yes. Dr. Stanek said

10 yes. Dr. Bennink said yes. Dr. Wharton said yes. Dr.

11 Monto said yes. Dr. Moore said yes. Dr. Edwards said yes.

12 Dr. El Sahly said yes. Dr. Janes said yes. Dr. Kotloff

13 said yes. Dr. McInnes said yes. So there are 11 or 12 --

14 11 unanimous.

15   DR. EDWARDS: So the next question will be for the

16 2017-2018 influenza vaccine to include A/Hong Kong H3N2-

17 like virus.

18   DR. ATREYA: Okay, again, Dr. Scott voted yes.

19 Dr. Stanek, yes. Dr. Bennink, yes. Dr. Wharton, yes. Dr.

20 Monto said yes. Dr. Moore abstained. Dr. Edwards said

21 yes. Dr. El Sahly said yes. Dr. Janes said yes. Dr.

22 Kotloff said yes. Dr. McInnes said yes. So there are 10

23 out of 11 said yes, and one abstention.

       DR. EDWARDS: Okay, the next vote will be for the

trivalent 2017-2018, the inclusion of the B/Brisbane

Victoria-like lineage.

       DR. ATREYA: Okay, once again, Dr. Scott said yes.

Dr. Stanek said yes. Dr. Bennink said yes. Dr. Wharton

said yes. Dr. Monto said yes. Dr. Moore said yes. Dr.

Edwards said yes. Dr. El Sahly, she abstained. Dr. Janes

said yes. Dr. Kotloff said yes. Dr. McInnes said yes. So

it's 10 out of 11 votes for this question.

       DR. EDWARDS: Thank you. For the final question

for the quadrivalent vaccine, does the committee recommend

the inclusion of B/Phuket in the vaccine?

       DR. ATREYA: Okay, once again, Dr. Scott said yes.

Dr. Stanek said yes. Dr. Bennink said yes. Dr. Wharton

said yes. Dr. Monto said yes. Dr. Moore said yes. Dr.

Edwards said yes. Dr. El Sahly said yes. Dr. Janes said

yes. Dr. Kotloff said yes. Dr. McInnes said yes. So

there are 11 out of 11, unanimous.

       DR. EDWARDS: So I think we have accomplished our

task today and thank you, everyone, for your participation

for the members and the guests, and hopefully we have

chosen the right strains.

       (Laughter.)

1   DR. ATREYA: Thank you all very much for your

2   participation. I appreciate it. This closes the meeting.

3   Meeting is adjourned.

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

5   adjourned.)