

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

1

FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

Friday, March 4, 2016

8:32 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Bldg. 31, Room 1503

Silver Spring, Maryland 20993

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

Reported by: Michael Farkas
Capital Reporting Company

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

2

APPEARANCES

MEMBERS :

Ruth Lynfield, M.D.

Acting Chair

Medical Director

Minnesota Department of Health

Mark Sawyer, M.D.

Professor of Clinical Pediatrics

University of California, San Diego

Patrick Moore, M.D.

American Cancer Society Professor

Distinguished Professor

Microbiology and Molecular Genetics

University of Pittsburgh Cancer Institute

Hillman Cancer Research Pavilion

Arnold Monto, M.D.

Professor of Public Health

Professor of Epidemiology

University of Michigan

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

3

MEMBERS :

Sarah Long, M.D.

Pediatrics and Infectious Diseases
Professor of Pediatrics
Drexel University College of Medicine
Chief, Section of Infectious Diseases
St. Christopher's Hospital for Children

Karen Kotloff, M.D.

Professor of Pediatrics and Medicine
Head, Division of Infectious Disease
Tropical Pediatrics
Associate Director, Clinical Research Center for Vaccine
Development
University of Maryland School of Medicine

TEMPORARY VOTING AND NON-VOTING MEMBERS :

Gillian Air, Ph.D.

Vice-Chair
Department of Biochemistry & Molecular Biology
University of Oklahoma Health Sciences Center
Department of Biochemistry and Molecular Biology

Ellen Andrews, Ph.D.

Executive Director
Connecticut Health Policy Project

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

4

TEMPORARY VOTING AND NON-VOTING MEMBERS:

Jack Bennink, Ph.D.

Chief, Viral Immunology Section
Laboratory of Viral Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Pamela McInnes, D.D.S., M.Sc. (Dent.)

Deputy Director
National Center for Advancing Translational Sciences
National Institutes of Health

Scott Stanek, D.O., M.P.H.

Colonel, US Army
Medical Countermeasures Directorate
Office of the Assistant
Secretary of Defense for Health Affairs

Melinda Wharton, M.D., M.P.H.

Deputy Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

5

TEMPORARY VOTING AND NON-VOTING MEMBERS:

Jerry Weir, Ph.D.

Director, Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Bruce Gellin, M.D., M.P.H.

Director National Vaccine Program
Office Health and Human Services

Judith Goldberg, Sc.D.

Professor of Biostatistics
Department of Population Health and Environmental Medicine
New York University School of Medicine

TEMPORARY INDUSTRY REPRESENTATIVE:

Filip Dubovsky, M.D., M.P.H., F.A.A.P.

Vice President
Clinical Biologics Therapeutic Area
Head, Infectious Disease and Vaccines
AstraZeneca/MedImmune, LLC

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

6

FDA ADMINISTRATIVE STAFF:

Designated Federal Officer

Sujata Vijh, Ph.D.

Division of Scientific Advisors and Consultants
Center for Biologics Evaluation and Research
Food and Drug Administration

Committee Management Specialist

Denise Royster

Division of Scientific Advisors and Consultants
Center for Biologics Evaluation and Research
Food and Drug Administration

SPEAKERS/PARTICIPANTS:

Anissa Cheung, M.Sc.

Regulatory Coordinator
Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Lisa Grohskopf, M.D., M.P.H.

CAPT, USPHS
Associate Chief for Policy and Liaison Activities
Epidemiology and Prevention Branch, Influenza Division
Center for Disease Control and Prevention

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

7

Jacqueline Katz, Ph.D.

Deputy Director (Acting) Influenza Division
Director WHO Collaborating Center for Surveillance
Epidemiology and Control of Influenza
Centers for Disease Control and Prevention

Michael Cooper, Ph.D.

CAPT, PHS
Leader, Respiratory Pillar Activities
Division of Global Emerging Infection Surveillance
Armed Forces Health Surveillance Center

Zhiping Ye, M.D., Ph.D.

Senior Investigator, Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Manju Joshi, Ph.D.

Lead Biologist
Division of Biological Standards & Quality
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration

Matthew Downham, Ph.D.

Associate Director, Biopharmaceutical Development
AstraZeneca/MedImmune

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

TABLE OF CONTENTS

AGENDA ITEM	PAGE
CALL TO ORDER AND OPENING REMARKS Ruth Lynfield, M.D.	10
INTRODUCTION OF COMMITTEE Committee Members	11
CONFLICT OF INTEREST STATEMENT Sujata Vijh, Ph.D.	15
TOPIC: STRAIN SELECTION FOR THE INFLUENZA VIRUS VACCINES FOR THE 2016-2017 INFLUENZA SEASON	
INTRODUCTION Anissa Cheung, M.Sc.	19
U.S. SURVEILLANCE Lisa Grohskopf, M.D., M.P.H.	27
WORLD SURVEILLANCE/VIRUS CHARACTERIZATION Jacqueline Katz, Ph.D.	44
BREAK	
DEPARTMENT OF DEFENSE VACCINE EFFECTIVENESS REPORT Michael Cooper, Ph.D.	86
VACCINE RESPONSES Zhiping Ye, M.D., Ph.D.	104
CANDIDATE VACCINE STRAINS & POTENCY REAGENTS Manju Joshi, Ph.D.	116
COMMENTS FROM MANUFACTURERS Matthew Downham, Ph.D.	125
OPEN PUBLIC HEARING ANNOUNCEMENT Ruth Lynfield, M.D.	143
OPEN PUBLIC HEARING Margaret Dayhoff-Brannigan, MD Patient Network Project Manager National Center for Health Research	144
COMMITTEE DISCUSSION	148
VOTING AND RECOMMENDATIONS	179
ADJOURNMENT	184

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

9

PROCEEDINGS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

OPENING REMARKS

DR. LYNFIELD: -- of the Vaccines and Related Biological Products Advisory Committee. And our topic today, of course, is "Strain Selection for the Influenza Virus Vaccines for the 2016-2017 Influenza Season." And I really appreciate everyone's work and expertise because this is such an important issue, so thank you all for coming. I really, again, would like welcome the members of the Committee, the participants, the public, and the audience, viewing the webcast.

I also want to extend a special welcome to Dr. Arnold Monto, who is a new member of VRBPAC. Welcome.

And I also want to note a few things. There are a number of folks, who are going to be joining us by phone today, and this includes Dr. Grohskopf, of the CDC, who will be presenting the U.S. data by phone.

I also want to mention that the Committee should be reminded not to discuss any of the topics outside of the open session, even at breaks, and at lunch. And I also would like to invite the members, consultants, FDA staff at the table, to now introduce themselves, we'll go around, and to state their

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

10

1 institutional affiliations. And so Dr. Sawyer, I wonder if we
2 can start with you.

3

4 **COMMITTEE INTRODUCTIONS**

5 DR. SAWYER: I'm Mark Sawyer. I'm a Professor of
6 Pediatrics, and Pediatric Infectious Disease Specialist, at the
7 University of California, San Diego.

8 DR. MOORE: I'm Patrick Moore, and I'm at the
9 University of Pittsburgh Cancer Institute.

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

14 DR. MONTTO: I'm Arnold Monto. I'm Professor of Public
15 Health and of Epidemiology in the School of Public Health,
16 University of Michigan.

17 DR. MCINNES: Pamela McInnes, Deputy Director,
18 National Center for Advancing Translational Sciences at the
19 National Institutes of Health.

20 DR. GRUBER: Marion Gruber, Director, Office of
21 Vaccines, Research, and Review at CBER/FDA.

22 DR. WEIR: Jerry Weir. I'm the Director of the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

11

1 Division of Viral Products at CBER/FDA.

2 DR. DUBOVSKY: My name is Filip Dubovsky. I'm a
3 pediatric infectious disease guy in preventive medicine. I
4 represent the industry. I work for MedImmune/AstraZeneca.

5 DR. BENNINK: Jack Bennink. The National Institute of
6 Allergy and Infectious Disease Intramural Research Program.

7 DR. ANDREWS: Ellen Andrews. I'm a consumer
8 representative, visiting for today, and I'm from the Connecticut
9 Health Policy Project.

10 COL. STANEK: Good morning. Colonel Scott Stanek.
11 Preventive medicine physician; Health Readiness, Policy, and
12 Oversight; Office of the Assistant Secretary of Defense for
13 Health Affairs.

14 DR. KATZ: Jackie Katz. I'm the Acting Deputy
15 Director of the Influenza Division at CDC, and the Director of
16 the WHO Collaborating Center for Influenza at CDC.

17 DR. WHARTON: I'm Melinda Wharton. I'm the Director
18 of the Immunization Services Division at the CDC.

19 DR. AIR: I'm Gillian Air, Professor of Biochemistry
20 at the University of Oklahoma, Health Sciences Center.

21 DR. GELLIN: I'm Bruce Gellin. I'm the Director of
22 the National Vaccine Program Office at HHS in Washington.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

12

1 DR. VIJH: Hi. This is Sujata Vijh. I'm the
2 Designated Federal Officer for the Vaccines and Related
3 Biological Products Committee.

4 DR. LYNFIELD: And Ruth Lynfield and I'm from the
5 Minnesota Department of Health.

6 Now, let's go to our folks on the phone.

7 DR. GOLDBERG: Okay. I'm Judith Goldberg. I'm a
8 Professor of Biostatistics at NYU School of Medicine.

9 DR. LYNFIELD: Great. Thank you for joining us.

10 DR. GROHSKOPF: I'm Lisa Grohskopf. I'm a medical
11 officer at the Influenza Division, CDC.

12 DR. LYNFIELD: Anyone else on the phone who is
13 participating?

14 (No response.)

15 DR. LYNFIELD: Okay. Well, thank you very much. I
16 appreciate all the introductions. And we look forward to very
17 important discussions today. And now I'd like to turn it over
18 to Dr. Vijh.

19 DR. VIJH: Thank you, Dr. Lynfield. Good morning
20 everyone. I'm Sujata Vijh. I'm the designated officer for
21 today's VRBPAC meeting. Ms. Denise Royster is the committee
22 management specialist for VRBPAC, and Ms. Rosanna Harvey is our

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

13

1 colleague, also, who is assisting us with the meeting today, and
2 you'll find them seated outside, if you have any questions.

3 On behalf of CBER, VRBPAC, as well as the Office of
4 Vaccines, we would like to welcome everyone to the 142nd VRBPAC
5 meeting today. As you know, Dr. Ruth Lynfield is the Acting
6 Chair for today's meeting. Dr. Katherine Edwards is the next
7 VRBPAC Chair, and she was unable to make it today, so Dr. Ruth
8 Lynfield is kindly serving as the Chair today.

9 Today's session has one topic that is open to the
10 public, in its entirety. The meeting topic is described in the
11 Federal Register Notice of January 6, 2016. The FDA and CBER
12 press media contact is Ms. Tara Goodin who is seated in the
13 audience.

14 Tara, could you please stand up? There's Tara. If
15 the press has any questions, please contact Tara.

16 Mr. Michael Farkas is the transcriptionist, who is
17 seated right there.

18 So when the speakers, please, use the microphones,
19 please press the microphone to talk, and remember to switch off
20 when you have finished speaking. Please speak clearly and
21 loudly into the microphone so that the transcriptionist, members
22 of the public, and those participating by phone, audience

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

14

1 listening on the webcast can hear your discussion. Please keep
2 your cell phones and pagers on silent mode.

3 And during an open public hearing, we request that the
4 people, who would like to make comments, please sign up on the
5 sheet placed here in the center of this aisle, so that we have
6 an idea, and please sign your name, as well as your affiliation.

7 We request that you, if you'd like to order lunch,
8 please do so at the kiosk outside, at the break, before 10:30
9 a.m., so that you don't have to wait in line because we have
10 another meeting going on next door.

11

12 **CONFLICT OF INTEREST STATEMENT**

13 At this point, I'd like to read the Conflict of
14 Interest Statement into the public record: "The Food and Drug
15 Administration is convening today, March 4, 2016, for a meeting
16 of the Vaccines and Related Biological Products Advisory
17 Committee under the authority of the Federal Advisory Committee
18 Act of 1972.

19 With the exception of the industry representative, all
20 participants of the Committee are special government employees,
21 or regular federal employees from other agencies, and are
22 subject to the federal conflict of interest laws and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

15

1 regulations.

2 The following information on the status of this
3 Advisory Committee's compliance with federal ethics and conflict
4 of interest laws, including, but not limited to, 18 U.S. Code
5 Section 208, being provided to participants at this meeting, and
6 to the public:

7 The FDA has determined that all members of this
8 Advisory Committee are in compliance with federal ethics and
9 conflict of interest laws. Under 18 U.S. Code Section 208,
10 Congress has authorized the FDA to grant waivers to special
11 government employees and regular government employees who have
12 financial conflicts, when it is determined that the agency's
13 need for a particular individual's service outweighs his or her
14 potential financial conflict of interest.

15 Related to the discussions to this meeting, members
16 and consultants of this Committee have been screened for
17 potential financial conflicts of interest, of their own, as well
18 as those imputed to them, including those of their spouse or
19 minor children, and for the purposes of U.S. Code Section 208,
20 their employers. These interests may include: investments,
21 consulting, expert witness testimony, contracts, grants,
22 CRADA's, teaching, speaking, writing, patents and royalties, and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

16

1 primary employment.

2 For the topic today, the Committee will discuss and
3 make recommendations on the selections of strains to be included
4 in the influenza virus vaccine for the 2016-2017 influenza
5 season. Based on the agenda, and all the financial interests
6 reported by members and consultants, no conflict of interest
7 waivers were issued under 18 U.S. Code Section 208.

8 Dr. Filip Dubovsky will serve as a temporary industry
9 representative today. Dr. Dubovsky is employed by
10 MedImmune/AstraZeneca. Industry representatives act on behalf
11 of all related industry.

12 Industry representatives are not special government
13 employees and they do not vote. They may be regulated industry
14 speakers and other outside organization speakers making
15 presentations. These speakers may have financial interests
16 associated with their employer and with other regulated firms.

17 The FDA asks that in the interest of fairness that
18 they address any current or previous financial involvement with
19 any firm whose product they may wish to comment upon. These
20 individuals were not screened by the FDA for conflicts of
21 interest. This Conflict of Interest Statement will be available
22 for viewing at the registration table.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

17

1 We would like to remind members, consultants, and
2 participants that if the discussions involve any other products
3 or firms not already on the agenda, for which an FDA participant
4 has a personal or imputed financial interest, the participants
5 need to exclude themselves from such involvement and their
6 exclusion will be noted for the record.

7 The FDA encourages all other participants to advise
8 the Committee of any financial relationships that you may have
9 with any firms, its products, and if known, its direct
10 competitors."

11 This concludes the reading of the Conflict of Interest
12 Statement for the public record. I now hand over the meeting to
13 Dr. Ruth Lynfield.

14 DR. LYNFIELD: Thank you, Dr. Vijh.

15 I also want to recognize an additional member of the
16 Committee. Dr. Kotloff, will you introduce yourself?

17 DR. KOTLOFF: Yes. I'm Karen Kotloff. I'm a
18 pediatric infectious disease physician at the University of
19 Maryland, School of Medicine.

20 DR. LYNFIELD: Thank you. Welcome.

21 Now, I would like to introduce our first speaker.
22 This is Ms. Anissa Cheung. The Regulatory Coordinator, Division

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

18

1 of Viral Products, Office of Vaccines Research and Review, at
2 CBER/FDA. And I'm wondering if Dr. Cheung can -- thank you very
3 much. Ms. Cheung, thank you very much.

4 STRAIN SELECTION FOR THE INFLUENZA VIRUS VACCINES

5 FOR THE 2016-2017 INFLUENZA SEASON

6 **INTRODUCTION**

7 MS. CHEUNG: Thank you and good morning everyone.

8 Today, I'm going to introduce the topics for today's
9 discussions. Okay. The purpose of today's VRBPAC discussions
10 is to review the influenza surveillance and epidemiology data,
11 and also, the antigenic characteristic of the recent ferret sera
12 isolates, the serological response to current vaccines, and the
13 availability of candidate vaccine strain and reagents.

14 And at the end of the discussions, this Committee the
15 VRBPAC will be asked to vote and make recommendations for the
16 strain of influenza A, both the H1N1 and the H3N2 and B viruses,
17 to be included in the 2016-2017 influenza vaccines license for
18 use in the United States.

19 So you are going to hear several presentations on the
20 data for the vaccine strain selections. And the types of
21 analysis used for vaccine strain selections that you are going
22 to be reviewing, include the epidemiology of the circulating

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

19

1 strains.

2 And the CDC folks will present surveillance data from
3 both the U.S., and around the world. You will also hear a
4 presentation on the antigenic relationships among the
5 contemporary viruses and the candidate vaccine strains. And you
6 will hear a presentation from CDC, the Department of Defense, as
7 well as, CBER.

8 And the types of assays and also techniques that you
9 will be reviewing include the hemagglutination inhibition test
10 using the post-infection ferret sera, and also a
11 hemagglutination inhibition test using panels of sera obtained
12 from humans that have received recent inactivated influenza
13 vaccines.

14 You will also hear some data on the virus
15 neutralization test, the antigenic cartography, as well as the
16 phylogenetic analysis of the HA and the NA genes of the recent
17 circulating virus, as well as the candidate vaccine virus. You
18 will also hear a couple reports on the vaccine's effectiveness.

19 There are several challenges for vaccine strain
20 selections. First of all, the vaccine effectiveness depends on
21 how well the match between the hemagglutination of the vaccine,
22 as well as the hemagglutination of the circulating strain of

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

20

1 viruses. However, the antigenic shift; there is an antigenic
2 drift of hemagglutinate that is continuous for both the
3 influenza A and the influenza B viruses, and for the inactivated
4 vaccines, as well as the recombinant protein vaccines, the
5 antibodies to hemagglutination are correlated with vaccine
6 efficacy.

7 Another challenge is the timeline for the influenza
8 vaccine production. It is relatively fixed, so it is necessary
9 to have to the strain selection done by February and early
10 March, in order to ensure the availability of the vaccines for
11 the subsequent northern hemisphere winter.

12 In fact, the manufacturers usually begin production of
13 monovalent of one strain at risk before strain selection
14 recommendations are made.

15 Another challenge is the availability of the reference
16 strain, which we also call "candidate vaccine viruses," which is
17 suitable for vaccine manufacture. And the vaccine production
18 depends on the growth properties of the strain. It depends on
19 how well the strain will be used for manufacture.

20 In addition, we also need to generate the strain-
21 specific reagents, which are needed for the potency
22 determination for inactivated and also recombinant protein

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

21

1 vaccines. So I would like to show you a graphical illustration,
2 to lay out in detail, month by month, to demonstrate to you how
3 rigid the production timeframe for seasonal influenza vaccines.

4 So you can see the strain selections have to be done
5 by February or early March, in order to have adequate time for
6 the generation of the referenced viruses, as well as the
7 production of the strain-specific reference reagent, for the
8 blending of the final vaccines, at the end of the day, to ensure
9 that we will have the availability of the vaccines to the public
10 for the northern hemisphere winter.

11 So we have both, the trivalent and quadrivalent
12 influenza vaccines available in the U.S. There are two
13 antigenically distinct lineages of influenza B that are co-
14 circulating, and they are represented by B/Victoria/2/87 and
15 also B/Yamagata/16/88. And you will hear people refer to it as
16 B/Victoria lineage as well as B/Yamagata lineage.

17 And currently, we have four quadrivalent vaccines
18 licensed in the U.S. And the current process for selecting an
19 appropriate B strain, for inclusion in the trivalent and
20 quadrivalent vaccines is similar to what we have done over the
21 years for the strain selection for the trivalent vaccine
22 recommendations.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

22

1 The WHO and the VRBPAC will review the data and make
2 recommendations for each formulation; for trivalent, as well as
3 quadrivalent. And we are expecting to have the same B strain
4 for the trivalent. So I want to quickly refer to the previous
5 recommendations, for the 2015 and 2016 vaccine strain
6 composition, for the northern hemisphere.

7 Exactly a year ago, the VRBPAC met and they
8 recommended the following strain for inclusion in the U.S. 2015-
9 2016 trivalent influenza vaccines:

10 For the H1N1 strain, the A/California/7/2009/pdm09-
11 like virus was being recommended, and there was no change from
12 the 2014 and 2015 vaccine recommendations;

13 For the H3N2 strain, this Committee recommended the
14 A/Switzerland/9715293/2013/H3N2-like virus. And there was a
15 change from the A/Texas/50/2012/H3N2-like virus from previous
16 recommendation;

17 For trivalent vaccines, the B strain included is
18 B/Phuket/3073/2013-like virus, which is from a B/Yamagata
19 lineage; and that was a change from the B/Massachusetts/2/2012-
20 like virus vaccine recommendations;

21 For a manufacturer producing quadrivalent influenza
22 vaccines, the Committee recommended a second B strain, which was

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

23

1 B/Brisbane/60/2008 from B/Victoria lineage; and this strain was
2 previously recommended for quadrivalent vaccines in 2014-2015.

3 The WHO also recommended a vaccine composition for the
4 southern hemisphere for 2016. In September 2015, the WHO met
5 and recommended the following viruses to be used for trivalent
6 influenza vaccines in the 2016 southern winter:

7 An A/California/7/2009/H1N1pdm09-like virus;

8 For H3N2, A/Hong Kong/4801/2014/H3N2-like virus; and

9 For B strain is B/Brisbane/60/2008-like virus, which
10 is from B/Victoria lineage;

11 It is also recommended that for quadrivalent vaccines
12 containing two influenza B viruses, contain the above three
13 viruses and also a B/Phuket/3073/2013-like virus, which is from
14 B/Yamagata lineage.

15 So I want to summarize where we are right now.

16 So a little bit over a week ago, the WHO also met in
17 Geneva, and recommended the vaccine composition for the northern
18 hemisphere 2016-2017. And WHO recommended the following viruses
19 to be used for the trivalent influenza vaccines in the 2016-2017
20 influenza season for the northern hemisphere:

21 A/California/7/2009 H1N1pdm09-like virus, which is no
22 change from the 2015-2016 northern hemisphere;

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

24

1 For H3N2 an A/Hong Kong/4801/2014/H3N2-like virus;
2 that is a change from the 2015-2016 northern hemisphere, but
3 this is the same strain recommended for the 2016 southern
4 hemisphere recommendation;

5 For B strain, they recommend a B/Brisbane/60/2008-like
6 virus from B/Victoria lineage; and that is a change from the
7 2015-2016 northern hemisphere recommendation; however, this
8 strain was previously recommended for quadrivalent vaccines.

9 WHO also recommended that for quadrivalent vaccines
10 containing two influenza B viruses, have to contain the above
11 three viruses, and also a B/Phuket/3703/2013-like virus, which
12 is a B/Yamagata lineage; and this strain was previously
13 recommended for trivalent vaccines.

14 As in the previous year, the national and regional
15 control authority is responsible to approve the composition and
16 formulation of vaccines used in their own country.

17 So now, I want to pause here, and I just want to let
18 you know that it's the role of this Committee VRBPAC to give
19 recommendations for the antigenic compositions of the 2016-2017
20 influenza vaccines in the U.S., so I would like to give you some
21 of the options for strain compositions for the 2016-2017
22 trivalent influenza vaccines:

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

25

1 For influenza A/H1N1, you can either recommend an
2 A/California/7/2009/H1N1/pdm09-like virus, which is the current
3 vaccine strain, or recommend an alternative H1N1 candidate
4 virus;

5 For the H3N2 influenza A virus, you can either
6 recommend an A/Hong Kong/4801/2014/H3N2-like virus, or recommend
7 an alternative H3N2 candidate vaccine virus;

8 For the B strain contained in the trivalent influenza
9 vaccines, you have three options:

10 (a) Recommend a B/Brisbane/60/2008-like virus from
11 B/Victoria lineage; or

12 (b) Recommend an alternative candidate vaccine virus
13 from the B/Victoria lineage; or

14 (c) Recommend a candidate vaccine virus from the
15 B/Yamagata lineage.

16 For strain selections for the second influenza B
17 strain in the quadrivalent influenza vaccines, you have two
18 options:

19 You can either recommend the inclusion of a
20 B/Phuket/3703/2013-like virus from B/Yamagata lineage; or

21 Recommend an alternative candidate vaccine virus from
22 the B/Yamagata lineage.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

26

1 So before I finish my introductions, I would like to
2 flush out the questions from the Committee, for the voting at
3 the end of the discussions. Thank you.

4 DR. LYNFIELD: Thank you very much, Ms. Cheung.
5 Are there any clarifying questions from the Committee?

6 (No response.)

7 DR. LYNFIELD: Okay. Thank you.

8 Now, I would like to introduce Dr. Lisa Grohskopf, who
9 is on the phone. And Dr. Lisa Grohskopf is from CDC, and she
10 will be presenting U.S. surveillance data.

11 DR. GROHSKOPF: Thank you. Can you hear me?

12 DR. LYNFIELD: Yes. Thank you very much.

13 DR. GROHSKOPF: Excellent. Thank you so much.

14

15 **U.S. SURVEILLANCE**

16 DR. GROHSKOPF: Good morning. I'm going to start with
17 the U.S. influenza surveillance update information. This
18 presentation is roughly divided in half; half a surveillance
19 update and half a vaccine effectiveness update. Next slide,
20 please.

21 So I'm going to start out with some surveillance data
22 for the National Respiratory Enteric Virus Surveillance System

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

27

1 and WHO collaborating laboratories. I should mention, just at
2 the beginning here. The data that I'm presenting here, in this
3 presentation, are from CDC's FluView. And unless otherwise
4 stated, are data for the week seven of the calendar year, which
5 is the week ending February 20, 2016.

6 I also want to mention that the data are updated each
7 Friday, and so these figures will be updated on the CDC's
8 FluView pages sometime later today.

9 So first, the U.S. Virologic Surveillance.

10 This slide and the one following, show results of
11 influenza-positive tests reported to CDC by WHO collaborating
12 laboratories and the National Respiratory and Enteric Virus
13 Surveillance System laboratories, all located in the United
14 States.

15 This first slide shows result's obtained from the
16 clinical laboratories in the system. In general, these
17 laboratories do not perform subtyping of influenza A viruses.

18 For our graph, the week of isolation is on the X axis.
19 And on the left Y axis, we have the number of positive
20 specimens, which is represented in the graph by the colored
21 bars. On the right Y axis, we have the percent of specimens
22 submitted that week that were positive, which is represented by

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

28

1 the black lines on the graph.

2 For the most recent week, week seven, 18,844 specimens
3 were tested, of which 2,599 or 13.8 percent were positive.

4 Influenza A viruses, which are depicted in yellow have
5 predominated, accounting for 76.1 percent of positive specimens
6 in week seven and overall 69.8 percent of specimens received
7 since October 4, 2015. Next slide.

8 Now, this slide summarizes the same information, but
9 this time for the public health laboratories rather than the
10 clinical laboratories that were on the earlier slide. These
11 labs generally perform subtyping of influenza A viruses. Some
12 do not, so that's why we still have some yellow representing the
13 un-typed A's up at the top of some of the bars here. And also,
14 some also will check lineage of B viruses.

15 Again, we see a predominance of influenza A viruses,
16 with H1N1/pdm09 in orange accounting for the majority of these.
17 Next slide.

18 Next, Virus Characterization of Influenza A Viruses:

19 Since October 1, 2015, the CDC characterized 660
20 influenza viruses collected by U.S. laboratories; these
21 included: 271 A/H1N1/pdm09 viruses; 242 A/H3N2 viruses; and 147
22 influenza B viruses;

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

29

1 All 271 influenza A/H1N1/pdm09 viruses were
2 antigenically characterized as A/California/7/2009-like;

3 All 242 (H3N2) viruses that were genetically sequenced
4 belonged to genetic groups for which a majority of viruses
5 antigenically characterized were similar to the cell-propagated
6 A/Switzerland/9715293/2013 virus;

7 Of 109 (H3N2) viruses, also antigenically
8 characterized, 102 or 93.5 percent were
9 A/Switzerland/9715293/2013-like by HI testing, or by
10 neutralization testing. Next slide.

11 For influenza B viruses, for the 147 of these
12 characterized, all 88 or 100 percent B/Yamagata lineage viruses,
13 were antigenically characterized as B/Phuket/3073/2013-like; 58
14 of 59 or 98.3 percent of the B/Victoria lineage viruses were
15 antigenically characterized as B/Brisbane/60/2008-like. Next
16 slide.

17 Next, Influenza-like Illness or "ILI" Surveillance
18 Data from the U.S. Outpatient Influenza-Like Illness
19 Surveillance Network or "ILINet:"

20 This slide summarizes data from 2015-2016, which is
21 shown in the line with the red triangles and selected previous
22 seasons. The calendar week is on the X axis, and presented

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

30

1 outpatient visits reported to be for ILI are on the Y axis;

2 ILI is defined as fever, that is a temperature of 100
3 degrees F or 37.8 degrees C or greater, and cough and/or sore
4 throat;

5 Nationwide, during week seven 3.2 percent of
6 outpatient visits reported through this system, were due to
7 influenza-like illness. This percentage is above the national
8 baseline of 2.1 percent. Next slide.

9 This slide summarizes hospitalization data from
10 FluSurv.NET:

11 FluSurv.NET covers more than 70 counties in the ten
12 Emerging Infections Program or "EIP" states, which are:
13 California, Colorado, Connecticut, Georgia, Maryland, Minnesota,
14 New Mexico, New York, Oregon, and Tennessee, and additional
15 Influenza Hospitalization Surveillance Project or IHSP" states;

16 Between October 1, 2015, and February 20, 2016, 1,594
17 lab-confirmed influenza-associated hospitalizations were
18 reported;

19 The overall hospitalization rate was 5.8 per 100,000-
20 population;

21 The highest rate of hospitalization was among adults,
22 age greater than or equal to 65 years, at 16.7 per 100,000-

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

31

1 population, and adults age 50 through 64 years, at 7.4 per
2 100,000-population;

3 Among all hospitalizations, 72.6 percent were
4 associated with influenza A; 25.7 percent with influenza B; 1.3
5 percent with A and B co-infection; and 0.4 percent had no virus-
6 type information;

7 Among those with influenza A subtype information, 89.0
8 were age A/H1N1/pdm09 and 46 or 11 percent were A/H3N2 viruses.

9 Next slide.

10 This figure depicts Surveillance of Pneumonia and
11 Influenza-Associated Deaths;

12 These data come from the National Center for Health
13 Statistics Mortality Surveillance System. In this case, these
14 data are from slightly earlier; the week ending February 6,
15 rather than February 20 of the calendar year, so this is really
16 more like week five data:

17 For week five 6.6 percent of deaths occurring,
18 reported to this system, the week ending February 6, 2016, were
19 due to pneumonia and influenza. This percentage is below the
20 epidemic threshold of 7.7 percent calculated for week five.

21 Next slide.

22 This slide summarizes Pediatric Deaths Associated with

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

32

1 Laboratory-Confirmed Influenza, which has been a reportable
2 condition since 2004; the graph depicts information from the
3 2012-2013 season, that's the cluster of bars on the far left, to
4 the present season 2015-2016, the smaller cluster of bars on the
5 right:

6 Thus far, a total, as of this week, of 14 influenza-
7 associated pediatric deaths have been reported during the 2015-
8 2016 Season. Next slide.

9 This is the last surveillance slide and it summarizes
10 Influenza Activity Reported by State and Territorial
11 Epidemiologists; it describes geographic spreads of influenza
12 viruses, but does not measure severity of influenza activity:

13 During week seven, widespread influenza activity was
14 reported by Guam, Puerto Rico, and 21 states;

15 Regional influenza activity was reported by 18 states;

16 Local influenza activity was reported by the District
17 of Columbia and 10 states; and

18 Sporadic influenza activity was reported by the U.S.
19 Virgin Islands, and one state. Next slide.

20 In summary, for the surveillance part of the talk:

21 Influenza activity, to date, is low, as compared with
22 the previous most recent three seasons;

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

33

1 Rates of influenza-associated hospitalizations are
2 lower;

3 Pneumonia and influenza mortality has not exceeded
4 threshold levels;

5 Influenza A/H1N1 viruses have predominated, but A/H3N2
6 and B viruses of both lineages have co-circulated;

7 The majority of viruses are similar to the current
8 vaccine viruses. Next slide.

9 So changing gears now and moving on to Interim
10 Estimates of Influenza Vaccine Effectiveness for this Season:

11 These data are from the U.S. Influenza Vaccine
12 Effectiveness, or U.S. Flu VE Network, and they were presented
13 recently at ACIP, which had a meeting on February 24, 2016;

14 These are preliminary interim estimates and have not
15 yet been published;

16 These particular interim estimates included patients
17 enrolled from November 2, 2015, through February 12, 2016. Next
18 slide.

19 Methods used by the U.S. Flu VE Network have
20 previously been described; methods used to produce these interim
21 estimates were the same as those used for interim estimates in
22 previous seasons:

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

34

1 Briefly, outpatients 6 months-of-age and older, with
2 acute respiratory illness and cough of seven or fewer days
3 duration, were enrolled at the five U.S. Flu VE Network sites,
4 from November 2, 2015, through February 12, 2016;

5 A test negative case control design was used to
6 estimate vaccine effectiveness, by comparing vaccination odds
7 among influenza RT-PCR positive cases, and RT-PCR negative
8 controls;

9 Vaccination status was defined at the receipt of at
10 least one dose, of any 2015-2016 seasonal influenza vaccine,
11 according to medical records, immunization registries and/or
12 self-report;

13 Vaccine effectiveness is estimated as one minus the
14 adjusted odds ratio times one hundred;

15 Variables included in the models for adjustment are
16 those listed. Next slide.

17 From November 2, 2015, through February 12, 2016, a
18 total of 3,333 outpatients were enrolled at the five network
19 sites:

20 Three thousand eighty-one or 92 percent were RT-PCR
21 negative for influenza;

22 Two hundred and fifty-two or 8 percent of enrolled

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

35

1 patients were influenza-positive;

2 Distribution of influenza cases by type and subtype is
3 shown: both influenza A and B viruses circulated with the
4 majority of influenza A viruses being H1N1/pdm09; and the
5 majority of B viruses belong to the Yamagata lineage. Next
6 slide.

7 This epi curve shows the number of enrolled
8 participants with RT-PCR-confirmed influenza A or B, by
9 epidemiologic week of enrollment and the percent positivity for
10 any influenza type by week; note that laboratory testing is
11 incomplete for patients enrolled during epidemiologic week six:

12 Few cases were enrolled before the first week of
13 January, with a low percentage of those enrolled being positive
14 for influenza A or B during most weeks. Next slide.

15 Interim-adjusted estimates of vaccine effectiveness
16 against medically-attended influenza for all patients, age 6
17 months and older was: 59 percent with a 95 percent confidence
18 interval from 44 percent to 70 percent. Next slide.

19 Interim-adjusted vaccine effectiveness against
20 H1N1/pdm09 for all ages combined was: 51 percent with a
21 confidence interval from 25 to 69 percent;

22 Adjusted estimates of vaccine effectiveness against

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

36

1 influenza B for all ages combined was: 76 percent with a
2 confidence interval from 59 to 86 percent, and was similar
3 against B/Yamagata lineage viruses at 79 percent. Next slide.

4 In summary, interim results from the U.S. Flu VE
5 Network for the 2015-2016 season, based on enrollment through
6 February 12, 2016, indicate vaccine effectiveness of 59 percent
7 against medically-attended influenza. The interim estimate for
8 this season is similar to that of previous seasons when vaccine
9 was well matched to circulating influenza viruses.

10 Significant protection against circulating influenza
11 H1N1/09 and B viruses was observed for all ages combined, while
12 VE was not estimated against the (H3N2) viruses, due to the
13 small number of cases. Enrollment in the network continues.

14 Interim estimates, it must be said, are less precise
15 due to the low numbers of flu cases enrolled, and end of season
16 VE estimates may differ from these interim estimates. Next
17 slide.

18 That concludes my presentation. I'd be happy to take
19 any questions. Thank you.

20 DR. LYNFIELD: Thank you very much, Dr. Grohskopf.

21 Are there clarifying questions? Yes?

22

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

37

1 **QUESTIONS:**

2 DR. BENNINK: In the vaccine effectiveness, is all of
3 that inactivated vaccine?

4 DR. GROHSKOPF: That is all vaccine. There is, at
5 this point, not sufficient information to be able to split data
6 out. As we've had relatively low numbers of cases, and
7 relatively low enrollment, given that the season's been a bit
8 slower than usual. I anticipate though, that information you
9 know should -- hopefully there should be enough cases in either
10 group to be able to split that out eventually.

11 DR. LYNFIELD: Dr. Grohskopf, I have a question; if we
12 could go back to slide three? I am wondering, what proportion
13 of B lineages are not characterized in that data set? Do you
14 have a rough ballpark?

15 DR. GROHSKOPF: I don't actually have that number in
16 my head. I don't know if Dr. Katz is aware of it. Those data
17 are represented by the dark green.

18 DR. LYNFIELD: Yes.

19 DR. GROHSKOPF: And you know it's -- obviously, that
20 proportion has increased somewhat, the overall number of
21 isolates have increased, but I actually don't know the precise
22 number. I can attempt to get that during today, though.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

38

1 DR. LYNFIELD: You know I think that would be helpful
2 because one of our questions is to choose the lineage for the
3 trivalent vaccine. And in looking at these data, it does appear
4 that the Yamagata lineage is making up a larger proportion than
5 the Victoria lineage. And so I think it would be useful to have
6 the proportion that is not characterized.

7 DR. GROHSKOPF: Okay. I will obtain that this
8 morning.

9 DR. LYNFIELD: Dr. Monto?

10 DR. MONTO: On slide four, you state that the (H3N2)
11 isolates are similar to the cell-propagated A/Switzerland. Are
12 we going to be hearing more about this issue, and the clades,
13 and everything else, because we're talking about a change, and
14 why a change, if everything's the same?

15 DR. GROHSKOPF: I believe that will be covered in the
16 data presented by Dr. Katz.

17 DR. LYNFIELD: Dr. Sawyer?

18 DR. SAWYER: Lisa, its Mark Sawyer. I noticed that
19 well, in 2009, when (H1N1) first began to circulate, it was the
20 younger adult population and pediatric population that had the
21 majority of disease. I notice from your epi curve, this season
22 so far, even though (H1N1) is the predominate A strain that the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

39

1 senior 65 and above are now more prominently featured with
2 medically-attended visits.

3 Are the numbers sufficient this year, so far, that you
4 anticipate that trend continuing? And if so, do you care to
5 speculate why, now, seniors are being more affected than younger
6 adults?

7 DR. GROHSKOPF: Difficult to speculate always, of
8 course. That is a great question. We did also, see sort of the
9 older/younger adults and the younger/adult older/adults those
10 groups of just below 65 and older, somewhat, were susceptible
11 during the 2013-2014 season with regard to hospitalizations, for
12 example, than they had in previous seasons, and 2013-2014 was
13 also an (H1N1) predominant season.

14 Difficult to say, really, I don't personally have an
15 explanation. Overall, the season did get off to a somewhat
16 later, slower start. It may be that we just are not seeing
17 sufficient numbers. I really do not have an explanation for
18 that.

19 DR. LONG: Hi Lisa. Sarah Long. I know your
20 definition of immunization, or vaccination was at least one dose
21 of the 2015-2016 seasonal flu vaccine, but if we think about the
22 circulation of pandemic 09, for the last several years, and the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

40

1 immunizations in the last several years containing that, do you
2 have any idea, or a speculation about how you might see
3 decreased vaccine efficacy because of widespread previous
4 immunization, or previous experience of those who are not
5 vaccinated this year? A complicated question, sorry.

6 DR. GROHSKOPF: Yes. I'm not exactly certain how to
7 address that. Of course, as those in the room know, H1N1/pdm,
8 or A/California/7/2009, has been present in the vaccine for some
9 time. Among those vaccinated repeatedly, they would have had
10 repeated exposure to that virus.

11 I guess one thing, I would want to be cautious about
12 is that the estimate that we're seeing now is, again,
13 preliminary and based on relatively fewer cases than we normally
14 have by this time of year. So I think it's you know at the end
15 of the day, going to be important to see what bears out in the
16 end as the season continues, and also once these data are more
17 finalized.

18 At present, for example, by the end of the season,
19 records have been gone through and self-report is less of an
20 issue, but up until this point as the season is going through,
21 particularly this early, immunization data is at least partially
22 self-report, by a greater proportion, with a somewhat lesser

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

41

1 proportion than there will ultimately be, coming from more
2 definitive sources.

3 Also again, we should in theory at least, have greater
4 numbers as time goes on. So I guess I would just be cautious
5 about understanding that these estimates are preliminary.

6 DR. LYNFIELD: Dr. Kotloff.

7 DR. KOTLOFF: Hi. It's Karen Kotloff. I notice that
8 your case definition was, "recipients of at least one dose," but
9 we know that for young children, the recommendation is for two
10 doses during the first vaccination series. And I'm wondering
11 what impact, you think were you to include young children who
12 had received the requisite two doses, what impact that would
13 have on your measured vaccine effectiveness?

14 DR. GROHSKOPF: I think at this point, it is difficult
15 to predict that. That information normally becomes available
16 more toward the end of the season. At this point, there
17 actually isn't even really sufficient data to break the cases
18 down by age distribution. So it would be difficult to speculate
19 on that right now.

20 DR. LYNFIELD: Dr. Moore?

21 DR. MOORE: Lisa, can you give us a little bit more
22 information on the (H3N2) vaccine efficacy, which you didn't

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

42

1 include in this presentation because the number of cases were so
2 small, but if we're going to be changing the vaccine component,
3 I'd like to get, at least, a little sense of, if we know where
4 the numbers are going, if we had enough numbers.

5 Were all 25 cases that were (H3N2) positive? Were
6 they unvaccinated or was it evenly distributed? Just, a little
7 bit more information on that.

8 DR. GROHSKOPF: I actually don't have that information
9 at hand, but I can put that on the list with the other questions
10 that came up about the distribution of B viruses in the
11 Virologic surveillance. And I will be on the phone all day, for
12 the entire meeting. So I will obtain, see if I can learn
13 anything else about that during the break, if that's all right.

14 DR. LYNFIELD: Thank you, Lisa, very much.

15 Are there any additional questions?

16 (No response.)

17 DR. LYNFIELD: Okay. Thank you very much, again.

18 DR. GROHSKOPF: Thank you.

19 DR. LYNFIELD: Now, I'd like to introduce Dr. Jackie
20 Katz, who will be presenting next. And Dr. Katz is the Deputy
21 Directing (Acting) of the Influenza Division, as well as the
22 Director of the WHO Collaborating Center for Surveillance,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

43

1 Epidemiology, and Control of Influenza, at the CDC. And Dr.
2 Katz is going to be speaking on world surveillance and virus
3 characterization.

4 DR. KATZ: Thank you, Dr. Lynfield.

5 Okay. So I'm going to be providing a summary of the
6 data that was presented last week at the WHO Vaccine
7 Consultation Meeting, for which the decision you've already
8 seen, was made for the WHO recommendations for the northern
9 hemisphere 2016-2017 influenza vaccine.

10

11 **WORLD SURVEILLANCE/VIRUS CHARACTERIZATION**

12 DR. KATZ: So surveillance, globally, for influenza,
13 is coordinated by the WHO Global Influenza Surveillance and
14 Response Network, also known as "GISRS." And as you can
15 appreciate, this is a year-round process, whereby, national
16 influenza centers and WHO Collaborating Centers, together with
17 the ERL's, the Essential Regulatory Laboratories, and other
18 reference laboratories, are continually performing surveillance
19 for seasonal and novel influenza viruses.

20 So as we've heard earlier from Ms. Cheung, there was a
21 decision for the southern hemisphere strain selection for 2016,
22 and that was made last September.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

44

1 So last week, the consultation included the review
2 analysis and a conclusion, over a three-day period. The meeting
3 was chaired by Dr. Yuelong Shu, from the China CDC, the WHO
4 Collaborating Center there, and included the nine advisors,
5 which represent the directors of the 6 WHO Collaborating
6 Centers, and directors of three essential regulatory
7 laboratories. There was also, another, about 25 people from
8 other national influenza centers, from other members of the WHO
9 Collaborating Centers, and ERL's, as well as academic partners,
10 and our partners from the veterinary sector, and other national
11 authorities.

12 So we've already heard that in September, the WHO
13 recommendations changed, and I just want to highlight why that
14 was done. The changes that were made were for the (H3N2)
15 component, which changed to A/Hong Kong/4801/2014; it was
16 previously Switzerland, for the 2015 southern hemisphere strain.

17 And that was really done, not because there was
18 recognition of antigenic drift, but because by September 2015,
19 there was availability of appropriate candidate vaccine viruses,
20 that more closely matched the genetic subgroup of circulating
21 viruses, and that virus was represented by the Hong Kong/4801,
22 so it was seen as sort of an incremental improvement for the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

45

1 (H3N2) component. The other change that was made was, to swap
2 the B lineage viruses around, and that was done in response to a
3 notable expansion of the B/Victoria lineage, represented by the
4 B/Brisbane/60/2008 component, and so it was felt that it was
5 more critical to have that B lineage in the trivalent
6 inactivated vaccine.

7 So moving on now to the data that we had for our
8 consultation and decision process last week. This is a WHO
9 slide showing the percentage of respiratory specimens that
10 tested positive for influenza by their transmission zones. And
11 there are two things to notice on this map.

12 First, is the shading, where you can see that shading
13 goes from sort of white, to light yellow, to a darker green, and
14 that represents an incremental increase in the number of
15 influenza positives. So you can see in North America, most
16 regions of North America, the activity and the numbers of
17 viruses isolated were lower than in some regions of Europe and
18 Asia. And then the pie charts represent the actual breakdown of
19 viruses by subtype and by B lineage.

20 And if you'll focus on the light blue, that's the
21 H1N1/pdm09 viruses, and you can see that they predominated in
22 many regions of the world. And this is shown here, over a time

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

46

1 series. This is the numbers of influenza viruses by subtype
2 that were identified globally to WHO, over the past year.

3 And as you can see, in sort of the late December,
4 towards the end of 2015, these numbers started to increase as
5 the northern hemisphere season took off, and is still sort of
6 peaking around this time. You can see, again, that the light
7 blue color represents the H1N1/pdm09 viruses, and they
8 represented the majority of viruses, and that's shown a little
9 more graphically here. You can see that about three quarters of
10 the viruses reported to WHO were influenza A, and of those, the
11 majority were (H1N1) with a smaller proportion being the
12 influenza B viruses.

13 So I'm going to talk now, first of all, about our
14 characterization of the H1N1/pdm09 viruses. So this is another
15 WHO slide that shows the activity level of (H1N1) worldwide
16 since September through, to early February. And what this map
17 represents is, actually it's sort of a heat map showing the
18 maximum activity reported over that time.

19 So we see that there are still some late season
20 southern hemisphere activity shown in Chile, and other regions,
21 for the southern hemisphere. But over the northern hemisphere
22 season, you can see that there was quite a lot of (H1N1)

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

47

1 activity, predominantly in parts of Europe, Africa, Asia, and
2 also widespread activity in North America, somewhat less so,
3 more localized activity, reported in the United States at that
4 time.

5 And just showing you another way, in looking at this
6 in terms of the last few seasons, you can see the red line,
7 which are (H1N1) viruses detected by the global system. For
8 2016, you can see that the number is quite high, and approaching
9 what was seen, in a big (H1N1) season in 2014, and much higher
10 compared with the black line, which was the 2014-2015 season in
11 the northern hemisphere.

12 So now we're going to start getting into some of the
13 technical genetic and antigenic data. And this is a tree of the
14 phylogenetic relationships of the hemagglutinin genes of
15 representative (H1N1) viruses. The color coding reflects the
16 month. And so the viruses colored in orange and pink, are the
17 most recently isolated or collected viruses, from January- -
18 February; in the green, are from December.

19 One thing to note is the current vaccine strain;
20 California/7/2009 is located here, and for the past several
21 seasons, we've seen that a group of genetic group 6B viruses
22 have predominated. But this season, we've seen quite the rapid

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

48

1 emergence of two genetic subgroup's within 6B, and these are the
2 6B1 viruses, which have these key amino acid changes at
3 residue's 84, 162, and 216 in HA1. And the change at 162
4 confers a glycosylation motif, which means that this site might
5 have a glycosylation added to it. And you can see that many of
6 the viruses are in this 6B1 cluster.

7 I know it's not possible to read this, from where you
8 are, but I do want to note that we have a number of viruses, and
9 this is true for all of our trees, that are annotated USAFSAM.
10 And this represents sequence's that have been contributed to the
11 system by our Department of Defense colleagues here in the U.S.
12 And these data are very useful to enrich, not only the data we
13 have for domestic viruses, but also from different international
14 sites. And you can see that -- well, you may not be able to
15 see, but I will tell you, that the viruses in the 6B1 group are
16 really from all parts of the world.

17 And similarly, there are also viruses from different
18 parts of the world, which fall into this smaller group; the 6B2
19 viruses. And they have represented genetic changes at residues
20 152 and 173, which are in the head of the HA1 molecule, and at
21 491 and 501, which are in the more-conserved HA2 region of the
22 molecule. So there are a smaller number of viruses here, but

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

49

1 geographically, most regions detected small numbers of these
2 viruses, also of the 6B2 group, with the exception of China,
3 that detected many such viruses, and you'll see the global
4 distribution in a further slide.

5 So this is also another way that we present the data.
6 This is done by our University of Cambridge modeling colleagues.
7 And so what they do, is they take all the genetic data for the
8 HA genes, that are available in our databases, and do a time
9 series over the last 11 months. And this has enabled us to
10 really see the rapid emergence of the 6B1 viruses.

11 Each virus is represented by a bar; they're color-
12 coded by the regions of the world that they come from. But the
13 main point I want to make here, is these last five or six months
14 since October, we've seen this very rapid emergence of the 6B1
15 viruses. The 6B2 viruses are down here; there's far fewer of
16 them, and they've really emerged since about July, of last year.

17 So we also look at the neuraminidase gene, and really
18 there are no dramatic changes there, but this is just to note
19 that, as for the hemagglutinin, the viruses are clustering into
20 different genetic subgroups.

21 So this is another way to look at the geographic
22 distribution of the (H1N1) viruses this season. And we can see,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

50

1 shown in orange, is this new genetic subgroup of 6B1 viruses.
2 And so it's very easy to see, that these viruses have been
3 predominating, in the viruses circulating in Europe, in North
4 America, and even in Oceania; although, the numbers are very
5 small because this isn't their flu season. We also see them in
6 Asia, but in Asia, there's also a substantial presence of the 6B
7 group, and this is largely driven by the predominance of the 6B2
8 subgroup in China. We're still seeing 6B viruses in South
9 America, and in Africa, but to a lesser extent.

10 Okay. I'm going to go through the first
11 hemagglutination inhibition test quite slowly. We've got some
12 more of these for the other influenza types and subtypes. So I
13 just want to orient you to what we do here.

14 So the hemagglutination test, tests the ability of
15 referenced panels of ferret antisera. And these are sera that
16 are raised, by infecting naïve ferrets, with the particular
17 virus in question. And ferrets make a very strain-specific
18 response, and they can uniquely characterize changes, antigenic
19 changes, in the hemagglutinin.

20 So the test measures the ability of these antibodies
21 present in the ferret's antisera, to block the interaction
22 between the virus and red blood cells. In this case, it's

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

51

1 turkey red blood cells, to which the virus binds through the
2 hemagglutinin. So the way this test is set up, is we have
3 different reference sera across the top. Shown highlighted
4 here, is the vaccine virus California/07, both an egg-grown
5 version and a cell-grown version; the homologous viruses under
6 the reference antigens, and so, the titer to its homologous
7 viruses, highlighted in red.

8 So we also have broken down the test viruses here, and
9 these viruses, many of them are from the U.S., they're also from
10 Central and South America and Asia, and a few from Europe.
11 We're showing the breakdown of the genetic groups here, and
12 these are the actual changes, but you can see that there are
13 many 6B1 viruses, and that's because that's primarily what we
14 saw circulating in the U.S.; still some 6B, and the occasional
15 6B2.

16 So when we look at how the test viruses react to the
17 sera, relative to the titer that we see, by, we get with the
18 homologous virus, we see for the California vaccine virus, that
19 all of the circulating tested viruses, are reacting to titers
20 that are very comparable to the homologous titers. So that
21 tells us that we're not really seeing any antigenic change,
22 compared with the California/07 vaccine virus.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

52

1 To further look at the antigenic properties of these
2 newly-circulating 6B1 and 6B2 genetic groups, we raised antisera
3 to representative viruses: the Michigan/45 virus for 6B1 and a
4 Minnesota/32 for the 6B2 groups. And these are highlighted in
5 the pink colors. And again, when you compare -- first of all,
6 these viruses are reacting comparably with the California/07
7 viruses, themselves, or these antisera are, and also they're
8 really, reacting very well with all of the circulating viruses.

9 So this tells us that these viruses, even when we look
10 at this in two ways, are not antigenically any different from
11 the California/07 viruses. So to look at this by another test,
12 we really wanted to confirm that the HI was showing us that
13 there were no antigenic differences. And so, on occasions we
14 have also used neutralization assays; we use these quite a lot
15 for the (H3N2) viruses.

16 So this is a neutralization assay that was performed
17 by the London WHO Collaborating Centre, known as the Crick
18 Institute. And this table is set up pretty much the same way
19 that the HI was. There are a more limited number of reference
20 antisera raised in ferrets, across the top, they're homologous
21 viruses. And the homologous titer's shown in red.

22 And then a number of circulating viruses that were

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

53

1 tested; these are from Europe. There's some from Iran, and one
2 from Africa in here. And again, these represent the circulating
3 viruses, some 6B1 virus; mostly 6B1, and one 6B2 here.

4 And we're essentially seeing the same result that we
5 saw with the HI. Antisera raised to the California vaccine
6 virus is reacting very well, and are comparable titers, in most
7 cases, for the circulating viruses. And when we raise an
8 antisera to one of these new genetic subgroups, this is a virus
9 called "Slovenia," we're seeing again, that compared with the
10 high homologous titer here, the circulating viruses are well
11 covered by this antisera.

12 We also do antigenic cartography, and this is done,
13 again, from our University of Cambridge colleagues. And they
14 are provided all of the HI data, from the WHO Collaborating
15 Centers. And in this particular depiction, the big red dot in
16 the middle represents the California/07 cell-grown; the egg-
17 grown is the green a little further away.

18 And what's being done here, is, there's color-coding
19 for the two genetic subgroups that we're currently seeing. So
20 in blue, is the 6B1, and in pink, is the 6B2. And you can see
21 that there's really, quite a tight clustering of these viruses
22 around the California/07 viruses, indicating that these viruses

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

54

1 are all antigenically very similar.

2 And then this is just the final information. This is
3 a compilation of the HI data, from all of the WHO Collaborating
4 Centers. You can see over 800 viruses were tested. And 99
5 percent of the viruses were antigenically characterized as being
6 California/07-like.

7 In summary, H1N1/pdm09 viruses were the most
8 frequently detected virus globally. The activity for (H1N1) was
9 generally higher than in the previous season, and there were
10 local-to-widespread outbreaks in many regions of the world. Can
11 you go back, please? Thanks.

12 And you may have heard reports in the media that there
13 were reports in Europe, from the Middle East, and also we've had
14 reports at CDC from the U.S., where there have been severe and
15 fatal cases reported. And that is really what we've seen in
16 previous years, when (H1N1) has circulated. And particularly,
17 in this year we know that about 50 percent of the H1N1/pdm09
18 viruses, the age range in 50 percent of those cases, has been in
19 the younger to middle-age adult, in that 24 to 50-plus age
20 group.

21 Of note this season, we have two new genetic sub-
22 clades that have emerged rapidly within the 6B group. The 6B1

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

55

1 viruses have expanded and are predominating in many countries of
2 the world. The 6B2 viruses have been detected at lower levels
3 in many countries, but are predominating in China. But
4 antigenically, all of these viruses remain similar to
5 California/7/2009.

6 We've also evaluated the neuraminidase inhibitor
7 activity, and the vast majority of (H1N1) tested were sensitive
8 to all of the neuraminidase inhibitors. So I'm going to move
9 on, to the (H3N2) viruses. This is the map of the world.

10 There's overall, lower activity. And again, some of
11 this activity is the late season from the southern hemisphere,
12 but there was some, local-to-widespread activity in North
13 America and Asia, and a few parts of some countries in Europe
14 and Africa.

15 And this sort of puts the influenza A activity this
16 season into perspective, particularly with last season, which is
17 shown in the black line. And you can see this is the current
18 season where there are overall, quite a small number of viruses
19 detected by the global influenza system.

20 Here again we have a phylogenetic tree of the
21 hemagglutinin gene. And the main point here is, as we saw last
22 season, we have several different genetic subgroups circulating.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

56

1 And the 3C2A viruses, in particular, continue to predominate
2 globally.

3 We've had a small resurgence of the 3C3A viruses. And
4 I'll remind you that the Switzerland/2013 vaccine component,
5 from our 2016-2017 season is a 3C3A virus. And then we have
6 some very low-level circulation still of the occasional 3C3 and
7 3C3B virus. So the Hong Kong/4801 virus that was selected for
8 the southern hemisphere 2016 is a 3C2A virus, and you can see it
9 highlighted here.

10 So among the recent viruses, there are two emerging
11 groups that have genetic changes. One is a group that has
12 changes at residues 142 and 197 in HA1, and many of these
13 viruses also have a change at 168. There's another group that
14 is expanding at this time, which has a substitution at 171, and
15 then several substitutions in HA2.

16 And when we look, we've been working with some
17 modelers to understand the trajectories and the expansions of
18 some of these subgroups. And we can see that the 171 group is
19 predominating in Asia and in North America, and continues to
20 expand at the moment. And there's also some expansion, to a
21 lesser extent, of this 142/197 group. So these are the groups
22 that I just want to highlight because we're also looking at them

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

57

1 antigenically, to see if they've changed at all.

2 This is another time series and this, just again,
3 graphically shows that really the 3C2A viruses are really still
4 predominating worldwide. There was as I mentioned, a slight
5 resurgence of 3C3A in Europe this season and very rare, if any,
6 circulation of the 3C3 and 3C3B in the northern hemisphere.

7 This is the neuraminidase gene, and again, the groups
8 that are defined by the hemagglutinin. You can see that the
9 viruses also break out into these groups for the neuraminidase
10 gene.

11 So looking at the global expansion, you can see a sea
12 of orange, and that tells you that the 3C2A viruses are
13 predominating in all parts of the world. As I mentioned, there
14 were some lower-level re-emergence of the 3C2A viruses, shown in
15 purple, in Europe, in the northern hemisphere, and then there
16 was also some activity in South America, and very little 3C3,
17 shown in the red, and 3C3B in the pink.

18 So before I talk about the antigenic characterization
19 of (H3N2) viruses, I just wanted to remind you that these
20 viruses have some very unique properties at the present time,
21 which makes them very technically difficult to do our standard
22 HI assay. First of all, we grow the viruses in mammalian cell

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

58

1 culture. Many of these viruses after repeated passage acquire
2 mutations in the neuraminidase at residues 151 or 148, and this
3 has been shown to enhance the ability of the neuraminidase to
4 actually bind to red blood cells. And so, that means that if we
5 just do a standard HI test, we don't know if when measuring
6 antibody to the neuraminidase, or antibody to the hemagglutinin.

7 So to rule out the binding to the neuraminidase, we
8 add the neuraminidase inhibitor, oseltamivir, and that
9 eliminates the binding ability of the neuraminidase, so we know
10 we're only testing antibodies that are binding the
11 hemagglutinin, and only characterizing that response. In
12 addition, in the last 18 months or so, many of the predominantly
13 circulating viruses, these 3C2A viruses, have, although they
14 will grow in cell culture, they bind the red blood cell
15 receptors very weakly. So we actually can't do hemagglutination
16 inhibition testing on about two thirds of the virus.

17 At CDC, we are able to test about one third of the
18 viruses that we grow in culture. And so we've been implementing
19 alternate assays, including the virus neutralization assay, and
20 so you'll see some virus neutralization results. In addition,
21 the 3C2A viruses have a glycosylation motif at the head of the
22 molecule, and with repeated passage in cell culture, all with

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

59

1 growth in embryonated eggs, they may lose this glycosylation.

2 I should say though, that for the majority of viruses
3 that we've tested at CDC by hemagglutination inhibition, we do
4 very limited passaging in cell culture. And over 80 percent of
5 the viruses have retained that glycosylation, so they do look
6 like the viruses, or like the sequence that we would get out of
7 an original specimen, out of the human.

8 So first of all, I'll show you a neutralization assay.
9 And this is again, data from the London Collaborating Centre.
10 So highlighted by the red bar, is the response of circulating
11 viruses. So this is set up the previous way of the previous
12 slides.

13 So across the top is, antisera to reference ferret
14 antisera. They're homologous viruses, and the homologous titers
15 shown in red. And then a number of circulating viruses; this is
16 mostly from Europe and Asia, and again, the different subclades
17 that these viruses belong to. And you can see a predominance of
18 3C2A, here.

19 And so if we look at this highlighted red box, here on
20 the right-hand side, this is ferret antisera raised to sell
21 propagated Switzerland. And you can see that with a homologous
22 titer of 160, that most of the circulating viruses have titers

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

60

1 that are within four-fold, and indeed within two-fold of this
2 homologous titer, indicating that they are well-covered by this
3 antisera to Switzerland.

4 If we look at the next red bar here, over on the left-
5 hand side, this is now, antisera, raised to sell propagated;
6 it's a Hong Kong/4801-like virus. It's not 4801 itself, because
7 of problems that we had in actually culturing the 4801 virus in
8 cells. So this is a surrogate for Hong Kong/4801-like virus.

9 And you can see, again, that the majority of viruses,
10 of the circulating viruses tested, are well-covered by this
11 antisera. And then shown in yellow is the results of the
12 antisera raised to the egg-propagated Hong Kong/4801 virus. And
13 most of the viruses are within four-fold titers of this
14 homologous titer; although, there are some reductions here. And
15 we particularly see reductions with the 3C2A viruses, and I'll
16 point that out a little more in the next test.

17 And this is another neutralization test. This is now
18 done at the CDC. We call it something slightly different, but
19 it's essentially a very similar neutralization assay as to the
20 one used in London.

21 The tables are set up the same way. And you can see
22 at the top, here, for our circulating viruses, we have a number

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

61

1 of viruses that are in this box that belong to the 3C3A group.
2 So highlighted in yellow, are the antisera to the Switzerland
3 viruses, both the cell-propagated and the egg-propagated
4 viruses, and again, you can see antisera to the cell-propagated
5 reacts very well, or within four-fold of the homologous titer,
6 with circulating viruses. The antisera to the egg-propagated
7 virus, does this a little less better, because it has a high
8 homologous titer.

9 If we look at the antisera raised to the 3C2A
10 referenced viruses, and these are the Hong Kong/4801 cell-
11 propagated and Hong Kong/4801 egg-propagated viruses, you can
12 see again that the antisera to the cell-propagated virus gives
13 titers to the circulating 3C2A viruses that are within four-fold
14 of this homologous titer. The responses, as I said, to the 3C3A
15 viruses, they're not as well-covered by antisera to the 3C2A
16 viruses.

17 And then when we look at this using antigenic
18 cartography, you can see -- this is data from the CDC
19 neutralization assays -- you can see that by this approach, the
20 viruses are really clustering around the Hong Kong/4801
21 reference viruses here, and 3C. So the 3C2A viruses are color-
22 coded in red and they're clustering around the 3C2A Hong

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

62

1 Kong/4801 virus. Obviously very small numbers of 3C3A viruses
2 shown in green and they're clustering more around the
3 Switzerland virus. So although we're not seeing a real
4 antigenic drift, we can distinguish between the 3C3A and 3C2A
5 viruses.

6 And this is a small HI test performed at CDC. One
7 thing I didn't mention in the early tables, but is also true for
8 this HI table, is, when we look at the viruses that have the
9 genetic changes that I referred to earlier, either the 142 or
10 197 changes, or some viruses with the 171 changes, we're not
11 seeing anything antigenically different, really, about these
12 viruses.

13 There is one virus here from Canada that is somewhat a
14 low reactor, but we believe that's because it has some other
15 unique changes in the hemagglutinin. So overall, although we're
16 seeing genetic changes, as we would expect in the (H3N2)
17 viruses, antigenically we're not seeing big differences in any
18 of these viruses that have these signature changes. And this is
19 shown again graphically.

20 So this is all of the CDC HI data that we have. And
21 similar to the neutralization antigenic cartography, you can see
22 that the 3C3A viruses shown in green -- and this is a time

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

63

1 series, so this is data from the last year, I believe -- you can
2 see that, although the 3C2A in red and 3C3A in green are
3 overlapping, the majority of 3C2A viruses are clustering more
4 around the Hong Kong/4801 virus, versus the Switzerland virus.

5 Was that, my time is up? No? Okay. I thought I
6 heard a bell go. Good. Okay. I've got time.

7 So what I'm going to show you in the next couple of
8 slides, is, all the HI data, from all of the collaborating
9 centers. The total number of viruses at the bottom is going to
10 change on each of the tables, just because at different times,
11 different centers, we're using different antisera to
12 characterize their viruses.

13 But if we look at antisera raised to the cell-
14 propagated Switzerland -- and I'll remind you that we have to
15 look at the antisera raised to a cell-propagated virus, because
16 most of our, or all of our test viruses, all of the circulating
17 viruses are grown in cells. And that's the best way to really
18 determine, whether there's antigenic drift occurring in the
19 circulating viruses.

20 We also compare results against egg-grown viruses, and
21 we do that because we have to propagate the viruses in eggs, in
22 order that we have a suitable candidate vaccine virus. But for

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

64

1 all influenza viruses, but particularly for (H3N2) viruses, egg
2 propagation leads to changes that may introduce some antigenic
3 changes. So first of all, I'm going to show you this table,
4 where you can see that -- can you go back to the previous table?

5 So compared with the antisera raised to Switzerland
6 cell-propagated reference virus, the vast majority of the almost
7 500 viruses tested, 97 percent remain similar to Switzerland,
8 which was the component of our vaccine this past season. And
9 there was a low proportion of what we would call "low reactors."

10 If we look at that in the same way, but now look at
11 antisera raised to the 3C2A virus Hong Kong/4801, we see the
12 same thing, which tells us that these viruses are really -- the
13 3C2A and the 3A, they're really not antigenically distinct. The
14 majority of viruses are also well-covered by antisera raised to
15 cell-propagated Hong Hong/4801.

16 If we now look at how circulating viruses react with
17 sera raised to egg-propagated Switzerland or Hong Kong, we see
18 that there's a trend towards the proportion of viruses that are
19 well-covered, or maybe I should refer to the ones that are not
20 reacting well with this antisera. So that's this column. We
21 refer to them as "low reactors."

22 They have titers that are reduced by at least eight-

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

65

1 fold to the homologous titer to Switzerland, and we can see that
2 we've got about 57 percent of the circulating viruses that were
3 tested by the different labs. However, if we look at the same
4 thing for Hong Kong, we can see that the antisera to the Hong
5 Kong/4801 3C2A virus, does a better job. There are a lower
6 proportion of viruses that are low reactors to this antisera,
7 suggesting that for an egg-propagated potential vaccine virus,
8 the Hong Kong/2014 viruses are providing better inhibition and
9 better coverage than are the Switzerland-like 3C2A viruses.

10 So in summary, there was, overall for (H3N2), there
11 was fairly low activity, particularly in relation to last season
12 and other seasons. The 3C2A viruses are now predominating in
13 all regions of the world, and the subclade 3C3A, although there
14 was a small resurgence in Europe, and the 3C3B viruses are
15 really circulating at quite low levels.

16 So most of the recent 3C2A viruses were well-inhibited
17 by ferret antisera raised against either the cell-propagated
18 reference Switzerland virus, or the Hong Kong virus. But I did
19 show you that the antisera to the 3C2A virus Hong Kong/4801-like
20 viruses, tended to have somewhat reduced inhibition against the
21 small number of 3C2A viruses that we could test. So we can
22 discriminate antigenically between these subclades in some

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

66

1 cases, but overall, they remain antigenically closely related.
2 When we look at ferret antisera raised to the egg-propagated
3 viruses, we see that the 3C2A virus, generally inhibit recently
4 circulating viruses better than antisera raised to the egg-
5 propagated Switzerland/2013 viruses, and then finally, again, we
6 really didn't see much evidence of resistance to the
7 neuraminidase inhibitors for the (H3N2) viruses.

8 So moving on to influenza B, this is, again, the heat
9 map from WHO, and you can see that there was some circulation of
10 influenza B viruses. And again, some of this is the late
11 southern hemisphere circulation, in the southern hemisphere, in
12 Oceania, and South America, but there was some activity in North
13 America, and in parts of Asia, and Europe, and Africa.

14 And so again, relative to previous seasons, you can
15 see overall that the 2016-2017 season in the northern hemisphere
16 for influenza B viruses, has been quite modest compared with the
17 previous several seasons, particularly 2015, in black.

18 And geographically, the distribution of the B/Yamagata
19 and B/Victoria lineages has changed. And so shown in orange,
20 are the B/Victoria lineage viruses, and you can see now that
21 they are predominating in many regions of the world. In
22 Australia and New Zealand towards the end of their southern

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

67

1 hemisphere season, the B/Victoria lineage really overtook the
2 B/Yamagata lineage.

3 The same thing was happening in South America. It's
4 very evident in Europe. It's in Asia and North America. The
5 B/Yamagata lineage shown in the blue is still predominating, but
6 we have seen an increase in the proportion of B/Victoria lineage
7 viruses this season in the United States.

8 So I'm going to first talk about the B/Yamagata
9 lineage viruses, and here's the genetic information from the
10 hemagglutinin. And just to point out, the B/Phuket/2013 vaccine
11 virus component is here, it belongs to the Y3 lineage, and you
12 can see that the vast majority of recently circulating viruses
13 around the globe belong to this Y3 lineage, and there's just a
14 very small number we detected.

15 We received some viruses from Africa that still were
16 the Y2 lineage, but this lineage, essentially appears to be
17 dying out. And this is one of the reasons that B/Phuket was
18 chosen a few seasons ago, to represent the B/Yamagata lineage.
19 So most of the circulating strains have this cluster of genetic
20 changes, and you can see some other changes spread out, but
21 there's really no further definition of genetic subgroups
22 emerging within the Y3 group.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

68

1 And this is just a time series. And it really
2 emphasizes that there was a lot of B/Yamagata virus activity in
3 the previous six months. And there's been a lower level of
4 activity in the current, just past six months, in all regions of
5 the world.

6 The neuraminidase tree there's really nothing
7 remarkable. I should go back and highlight. I forgot to
8 mention that we continue to see the persistence of some
9 interesting viruses that are reassortants between the B/Yamagata
10 lineage and the B/Victoria lineage, so they have the
11 hemagglutinin of the Yamagata lineage, the Y3 group, but they
12 have the neuraminidase of the B/Victoria group, the V1A
13 subgroup.

14 So these are still circulating. We see them in the
15 U.S. There are several viruses here, from the U.S., and we see
16 them in other parts of the world, also, in Asia, and Africa, and
17 other regions, but they remain at a fairly low consistent level.

18 So just moving on to the hemagglutination inhibition
19 test, that we use for influenza B viruses; again, the reference
20 viruses. The antisera to the reference viruses are across the
21 top. These are the homologous viruses, and their titers are
22 shown in red on the diagonal. And highlighted in yellow, are

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

69

1 the results with the antisera raised to either a cell-propagated
2 or an egg-propagated B/Phuket/3073 virus.

3 And you can see that all of the circulating viruses --
4 and we have viruses here, many of them from the U.S., we have
5 some from Bangladesh, and some from Africa here. And again, the
6 majority of these are Y3. We have some of these reassortant
7 viruses in there, and even some of the Y2 viruses.

8 The vast majority or all of these viruses are actually
9 reacting to the antisera to B/Phuket at titers that are within
10 four-fold of the homologous titer. And that tells us that they
11 are antigenically similar to the B/Phuket viruses.

12 So looking at this for antigenic cartography and this
13 is just showing now -- this is color-coded. So this is all HI
14 data from over this time period, and you can see that the more
15 recent viruses from September 2015 onwards, are colored in
16 yellow and the older viruses are colored in blue. And you can
17 see that the more recent viruses, like the older viruses are
18 still clustering very tightly near the B/Phuket reference
19 viruses, both the cell and the egg-propagated viruses.

20 And this is the summary table of almost 600 viruses
21 tested by all of the collaborating centers. And overall, 99
22 percent of these viruses were characterized as being

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

70

1 B/Phuket/3073/2013-like, so antigenically similar to the
2 B/Phuket vaccine component. For the B/Victoria lineages, again
3 these viruses are co-circulating with B/Yamagata, and in many
4 cases are predominating now.

5 They all still belong to the V1A genetic subgroup, as
6 does the B/Brisbane/60/2008 vaccine component for the B/Victoria
7 lineage. These viruses that are circulating now have changes at
8 residues 129, 117, and 146, compared with the older viruses, but
9 they all still fall into the V1A lineage. And again, you can
10 see very recent viruses from January and February, and there's
11 really nothing new to report genetically with these viruses.

12 This is just, again the time series and you can see
13 down here, these new groups that contain the 117V change. That
14 really these are the predominating viruses right now, in the
15 last several months.

16 For the neuraminidase, we do see this subgroup here
17 that I mentioned in the previous slides. So this is the
18 B/Yamagata lineage viruses that have the Yamagata HA, but they
19 have the neuraminidase of the B/Victoria lineage. And
20 otherwise, there's really nothing to really note with the
21 neuraminidase.

22 So looking at the antigenic characterization of these

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

71

1 viruses by hemagglutination inhibition test, this is a CDC test,
2 and you can see, so genetically these viruses are all V1A
3 viruses. And shown highlighted in yellow on the left-hand side,
4 is the antisera that are raised to the egg-propagated
5 Brisbane/60 and its cell-grown counterpart. And you can see
6 that the antisera raised to the cell-grown virus, covers very
7 well all of the circulating viruses tested. The antisera raised
8 to the egg-propagated, we do see some four-fold reductions, but
9 that's still considered to be antigenically-like the
10 B/Brisbane/60 virus.

11 And then, again, just showing the antigenic
12 cartography, again, the majority of these viruses of the more
13 recently circulating viruses shown in yellow, are clustering
14 very closely to the B/Brisbane. I should have mentioned, on the
15 previous slide, also -- I'm sorry to jump around a bit -- but I
16 should have mentioned also, the reactivity with the Texas
17 antisera shown here. It's not highlighted, but you can see,
18 that antisera raised to the Texas/02 reference virus is also --
19 very well covers the circulating viruses. And Texas/02 is a
20 candidate vaccine virus that is Brisbane/60-like, it's just a
21 more recent B/Victoria V1A lineage virus.

22 And finally, of about 500 viruses that were

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

72

1 characterized from the B/Victoria lineage, by the different
2 global laboratories, we see again that 96 percent of them are
3 characterized as being B/Brisbane-like, similar to the
4 B/Victoria lineage component of current vaccines, and only 4
5 percent showed reduced reactivity.

6 So in conclusion for the influenza B viruses,
7 B/Victoria and B/Yamagata lineage viruses have co-circulated,
8 but it's clear that B/Victoria lineage viruses are predominating
9 in many countries, or where they're not yet predominating, they
10 certainly have increased their proportions, as we have seen, for
11 example, in the U.S. this season.

12 For the B/Yamagata lineage viruses, the vast majority
13 of viruses belong to the genetic clade Y3, and only a very small
14 number, now, belong to clade 2. And all the recently
15 circulating viruses are well-inhibited by ferret antisera raised
16 against either the egg or cell propagated B/Phuket/3073/2013
17 virus.

18 For the B/Victoria lineage, all the viruses have
19 hemagglutinin genes that fall into the clade 1A. And again,
20 recently circulating viruses are well-inhibited by ferret anti
21 sera raised to either the Brisbane/60/2008 or the B/Texas/2/2013
22 viruses, representing the candidate vaccine viruses that are

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

73

1 available. And again, the majority of influenza B viruses that
2 were tested were sensitive to neuraminidase inhibitors.

3 So as you've already seen from Ms. Cheung's
4 presentation, based on the data that I've just shown you, last
5 week the WHO group recommended the following composition for the
6 2016-2017 Northern Hemisphere season:

7 They recommended a California/7/2009-like virus for
8 the H1N1/pdm09 component;

9 A/Hong Kong/4801/2015-like virus for the (H3N2)
10 component;

11 For the trivalent vaccines, the B/Brisbane/60/2008-
12 like virus representing the B/Victoria lineage;

13 For quadrivalent vaccines, the additional B component
14 would be the B/Phuket/3073/2013 representing the B/Yamagata
15 lineage.

16 And so I'd just finally, like to acknowledge all the
17 people who contributed: these are the collaborating centers
18 from Beijing, Melbourne, London, Tokyo, as well as Geneva staff;
19 the Global Influenza Surveillance and System, which is comprised
20 of about 143 national influenza centers in 113 countries, and we
21 really couldn't do this work without the provision of viruses
22 through this system, and it's just a fabulous effort every year;

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

74

1 Also, the University of Cambridge partners that
2 provide important visualization of our data; the essential
3 regulatory laboratories, as we'll hear from Dr. Zhiping Ye,
4 later on, there's another component to the testing that we do,
5 and he will provide the results of the serologic testing,
6 looking at human sera;

7 We also have many U.S. partners; the APHL, as I
8 mentioned earlier, our colleagues from DOD, who provide
9 sequenced data for us and really enrich the data sets that we
10 have, and also just a lot of people at CDC at the Collaborating
11 Centers; and I'd just like to call out Dr. Xiyan Xu, who runs
12 our virus reference team, who does most of this data analysis
13 and collection, and she's here today; she's also the Deputy
14 Director of our Collaborating Centre. Thank you.

15 DR. LYNFIELD: Questions?

16

17 **QUESTIONS**

18 UNIDENTIFIED PERSON: Yeah. Excuse me. I have a few
19 here. The first one is, really, to go back to your point
20 before, in terms of why the Brisbane, and not the Phuket in the
21 trivalent. I mean in the U.S., it was, in the other data, it
22 was 24 versus 17 percent. And here, globally it's 3 versus 2,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

75

1 so still more predominant or I think that was on one of the --
2 it's okay, it's one of the early slides, I saw it. The other
3 thing is, in the egg-grown Brisbane --

4 DR. LYNFIELD: Slide six.

5 DR. MOORE: In the egg-grown Brisbane, it's less of a
6 match even than the Brisbane that's in the cartography, at
7 least; it was on 52, or something like that, but you can go to
8 this slide first.

9 DR. KATZ: Right. But, this is just what's reported
10 to WHO. I think a better representation of what we're seeing,
11 can really be seen with the sequence data, because the sequence
12 data really demonstrates that the B/Victoria lineage is
13 predominate, or has emerged to predominate in multiple regions.
14 And if you'll recall, I don't know if we can go to that slide.

15 It was one of the last slides. It's probably around
16 slide 50 or so. Go back. No it's more like 45. Keep going.
17 There that one. Thanks.

18 So if we look by genetic groups, and this may not have
19 been quite clear because of the labeling, but the orange
20 represents the B/Victoria lineage, that is, the genetic grouping
21 of the B/Victoria lineage that's now circulating. And you can
22 see, again, the numbers are small for Oceania, for the September

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

76

1 period, but starting last July or August, in the middle of their
2 season, they really saw this switch to the B/Victoria lineage.

3 It was also seen in this season in Europe, it's very
4 clearly seen. There's a greater proportion of B/Victoria,
5 although it's not the majority yet in Asia, and it's turning
6 that way too, in the U.S. Last season, it was like three-to-one
7 and it's expanding. So I take your point, but I think on the
8 global level, I think we all think that -- and we know that the
9 B/Yamagata and the B/Victoria lineage viruses, you know every
10 few years switch backwards and forwards.

11 And we've certainly had the B/Yamagata lineage
12 predominating globally for several seasons, so I think the
13 experts felt that the B/Victoria's time was coming, and it was
14 switching back toward B/Victoria.

15 Dr. MOORE: Okay. And a next question is going to the
16 Hong Kong-like virus, but the term "like" in this particular
17 case. Clearly, from the antigenic data and the other, that the
18 Hong Kong itself is closer or better, particularly for the egg-
19 grown virus, okay, than if you used a -- what -- at least the
20 way I presume it, a "like" virus, such as Switzerland, or
21 something else.

22 DR. KATZ: Actually, Switzerland is not a Hong

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

77

1 Hong/4801-like virus --

2 Dr. MOORE: Okay.

3 DR. KATZ: -- because it's 3C3A, and antigenically, we
4 can discriminate those a little better.

5 DR. MOORE: So what would be included within the term,
6 "like" in this particular case, as well? I thought that the --
7 some of these --

8 DR. KATZ: So for Hong Kong/4801, it includes cell-
9 propagated viruses. And I didn't call out the actual names of
10 all the viruses because I thought it might get a bit too
11 confusing. But for example, the different centers use different
12 cell-propagated viruses that are Hong Kong/4801-like, and we use
13 a virus from Michigan.

14 The London group uses another Hong Kong virus, and so
15 there's a series of viruses that when we test them
16 antigenically, they meet the criteria, that we can call them
17 "like." And so, because of the difficulties with (H3N2)
18 viruses, we can't all be using Hong Kong/4801, especially for
19 cell-propagated because of the challenges with the properties of
20 these viruses in cell culture.

21 Dr. MOORE: One final question that I probably should
22 last -- Gillian asked this, or something like this, but where

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

78

1 the NA is beginning to bind cells and other things that way, do
2 you have any evidence or anything that anti NA antibodies then,
3 become more effective in terms of the vaccines or anything else?

4 DR. KATZ: We don't have evidence for that. And
5 really, we think that this is a cell culture phenomenon, because
6 when we look at the original clinical samples, we don't see this
7 heterogeneity in the neuraminidase. We see it when we culture
8 the virus, primarily in MDCK cells.

9 And that was one reason, and I probably didn't give a
10 full explanation of this either -- we've changed. We've moved
11 to -- they're still Madin-Darby canine kidney cells, but they're
12 a cell line called "SIAT" which have been engineered to express
13 a little more of the receptor that human viruses like to bind
14 to.

15 And when we use that cell line, we don't see so much
16 of these changes in the neuraminidase, so we don't think that
17 this is necessarily happening in a clinical sample or in a
18 person. It's happening because we culture these viruses in
19 order to try and characterize them antigenically. And so we've
20 done these various manipulations including using the
21 neuraminidase inhibitor to block that reactivity.

22 It's a very good question about the role of antibodies

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

79

1 to neuraminidase, in terms of protection, and whether vaccines
2 should be more focused on that, but I think it's a topic for
3 different day.

4 DR. LYNFIELD: Dr. Monto?

5 DR. MONTO: I think your question about neuraminidase
6 antibodies, it is relevant because we have published with Jackie
7 on the independent protection that neuraminidase does give in
8 humans, based on some vaccine effectiveness studies that we've
9 been doing. I think we have, as Jackie well knows, a semantic
10 problem.

11 When we say, as in the previous presentation, that all
12 of the viruses this year are A/Switzerland-like, when in fact
13 they don't belong to the clade that A/Switzerland belongs to --
14 neither were they last year. All of the viruses we had, and we
15 had a lot of failures, were 3C2A. And we know that everybody
16 who failed, had high antibody titers, not only to the vaccine
17 strain, which was A/Texas, but also to A/Switzerland.

18 This shows the real problem we have with A3 and 2, in
19 terms of protection. Every time we do vaccine effectiveness
20 studies, the best protection is against the B, that we worry so
21 much about, in terms of trying to guess, which is going to be
22 the predominant strain.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

80

1 Next, is (H1N1) and even in well-matched years, it's
2 (H3N2). And I think we really have issues to address with
3 (H3N2), which -- and this is not the time, or the place for
4 further discussion of those issues, but I think we have some
5 real issues there.

6 Dr. ANDREWS: This is new for me, but I think I've
7 been following it. I was really struck by the geographic
8 differences for all of them, especially (H1N1) the most common,
9 and I wonder what other countries, are making decisions right
10 now, are they following the WHO? Are they crafting it for what
11 they're seeing where they are?

12 And also, do we have regional differences? I mean, we
13 do in the spread of the virus across the United States. Are
14 there differences in the type that -- I get that you know virus
15 types work, if you immunize someone against one type, it works
16 to some extent, against others. And I get you have to grow it,
17 which so takes me back, the troubles of growing a virus, but how
18 do you take all those pieces, and craft it into a WHO
19 recommendation and whether the United States should do the same
20 thing?

21 DR. KATZ: Yeah. I think that's I guess, something
22 that you guys will decide. But the Europeans will make a

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

81

1 decision in; I think it's another couple of weeks, the same with
2 Japan. I'm not sure what other national authorities do, maybe
3 our folks at CBER know that a little better, but they certainly
4 take into account the WHO data.

5 It is very hard to predict from year to year, what's
6 going to spread and what's going to circulate in a certain
7 region. I mean there was Italy; in the middle of Europe was a
8 standout, that it didn't have a lot of H1's. It had more H3's
9 this year, apparently. So it's hard to predict, but I think you
10 really need to go with the global picture.

11 Last year we saw in our USV network, we saw some
12 interesting, very small, focused regional circulation of a
13 particular genetic subgroup of (H3N2). And this season it's too
14 early to tell, but at least we know that all the viruses in the
15 U.S., are really, for the H3's, are 3C2A, the vast majority, and
16 we know for the (H1N1)s, that the 6B1 genetic group is
17 predominating.

18 DR. LYNFIELD: Jackie, I have two clarifying
19 questions. One is, as long as we have slide 39 up, do you have
20 a sense of the temporal change in Victoria versus Yamagata?
21 When you were speaking, it sounded like, over time, Victoria
22 came out, and so I just wanted to confirm that.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

82

1 And also, in those areas where influenza has peaked,
2 we've kind of had a late season. Can you comment specifically
3 on that interaction with Victoria and Yamagata?

4 DR. KATZ: Yeah. So I think I can say, that it was
5 very noticeable at the September WHO Vaccine Consultation, which
6 was making recommendations for this year's southern hemisphere
7 season. There really was a swing in southern hemisphere
8 reporting of the B/Victoria lineage, so I would say it was
9 starting to take off at that time. The B/Victoria lineage was
10 starting to overtake the B/Yamagata lineage, in regions in the
11 southern hemisphere. And then we've seen the same thing, quite
12 dramatically in Europe, and it's increasing in proportions in
13 North America, and in South America also, so I'd say, since sort
14 of the middle of 2015, this has been happening.

15 With respect to seasonality, I guess -- I mean with
16 respect to sort of the late season, we sometimes do see the B's
17 emerge you know later in the season. We're clearly not done
18 with our season yet, so it's hard to predict, but certainly with
19 the numbers of viruses we're seeing in the U.S. at the moment.
20 We're seeing more, as I said earlier, it was more, 75 percent or
21 so Yamagata, 25 percent B/Victoria last season, and it seems
22 that the B/Victoria is expanding at this time. Whether we'll

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

83

1 see further expansion of those numbers, as the season continues
2 and tails off --

3 DR. LYNFIELD: It's hard to know.

4 DR. KATZ: -- it's hard to say.

5 DR. LYNFIELD: Right. And then if we could go to
6 slide 52, for a moment? So I was just wondering if you could
7 go through this slide again, because it looks like you know
8 there's a bit of a difference between the egg-grown Brisbane and
9 the cell-grown Brisbane. We don't have a cell for Texas in
10 there, and I'm not sure which the Malaysia is, but I was
11 wondering if you could just discuss this slide a little bit
12 more.

13 DR. KATZ: Right. Okay. So the B/Malaysia is an
14 older strain, it just is to demonstrate an earlier --

15 DR. LYNFIELD: Yes.

16 DR. KATZ: -- an earlier virus. So it's not really
17 relevant. So in our hands, the B/Brisbane, any sera to
18 B/Brisbane cell-propagated and egg-propagated, cover the
19 circulating viruses quite well. We have seen that there is in
20 some cases, a four-fold reduction in titer response, relative to
21 Brisbane egg-grown.

22 In other centers, and I think this might be some

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

84

1 cumulative data of the different centers, so it's not just our
2 data; in other centers, they see bigger differences with the
3 B/Brisbane egg. And they are reporting their antigenic
4 characterization based on antisera raised to Brisbane cell-
5 propagated.

6 In different centers, there are unique -- each ferret
7 antisera has a unique property, and sometimes, if antisera has a
8 very high homologous titer, it has the appearance that there is
9 antigenic difference, and that's another reason that we always
10 have to you know take a step back, and look at the response
11 relative to the cell propagated. And that's what we're doing
12 here.

13 And so the distance with the B/Texas egg-propagated
14 this year, was something that we saw in our laboratory. So I
15 showed you on the HI table that the circulating viruses reacted
16 very well with antisera to the Texas cell-propagated, but we had
17 again, the situation where our antisera to the Texas egg-
18 propagated virus had a very high homologous titer, so it made it
19 look like viruses were not reacting as well. And that's
20 probably why it looks like there's this distance in this
21 particular antigenic cartography. But the viruses were actually
22 from all laboratories, still showed good antigenic similarity

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

85

1 with Brisbane cell-propagated viruses, and that was across the
2 board.

3 DR. LYNFIELD: Thank you.

4 DR. LYNFIELD: Any other clarifying questions?

5 (No response.)

6 DR. LYNFIELD: Okay. Then thank you very much, Dr.
7 Katz.

8 It is time for our break. And can we give until 10:40
9 a.m.

10 DR. VIJH: That's up to you to say.

11 DR. LYNFIELD: Okay. Let's come back at 10:40 a.m.

12 **BREAK**

13 DR. LYNFIELD: ... Dr. Cooper, who leads the Respiratory
14 Pillar Activities, at the Division of Global Emerging Infection
15 Surveillance, and Dr. Cooper will be speaking to us on the
16 Department of Defense Vaccine Effectiveness report.

17 Great. Dr. Cooper.

18 DR. COOPER: Is this thing on? All right good.

19
20 DEPARTMENT OF DEFENSE VACCINE EFFECTIVENESS REPORT

21 DR. COOPER: Good morning. As mentioned, my name is
22 Michael Cooper, and I am the pillar lead for the Respiratory

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

86

1 Surveillance Pillar at GEIS, which is, Global Emerging Infection
2 Surveillance and Response Section of the Armed Forces Health
3 Surveillance branch. As you've probably deduced, we are a DOD
4 asset.

5 So today, I'll be presenting data on the 2015-2016
6 influenza season from our influenza surveillance network;
7 included here, will be surveillance data from our partners in
8 North America, Asia, Europe, and Egypt. In addition,
9 surveillance data will also be presented on our recruit
10 population within the United States.

11 I'll also be presenting a brief summary of the
12 phylogenetic analysis developed by our partners at the U.S. Air
13 Force School of Air Space Medicine. These analyses were already
14 covered in some detail by Dr. Katz in her briefing, so I will
15 not spend a lot of time on that.

16 In addition, I'll be presenting free midyear vaccine
17 effectiveness estimates, developed by our partners at the Naval
18 Health Research Center, NHRC, in San Diego; the United States
19 Air Force School of Aerospace Medicine, USAFSAM, and our Epi
20 Analysis Section at the Armed Forces Health Surveillance Branch.

21 (Pause.)

22 My disclaimer.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

87

1 (Pause.)

2 All right. So as I mentioned, GEIS has a fairly
3 extensive respiratory disease surveillance program. We have
4 about 400 locations in over 30 countries. We are dedicated to
5 the surveillance of military populations, but not exclusively.
6 We also have relationships with foreign ministries of health,
7 foreign ministries of defense, and academic institutions, which
8 enable us to do surveillance on local national populations,
9 foreign local national populations.

10 We have extensive characterization capabilities,
11 including sequencing, PCR, and culture, and we share our results
12 with the CDC and WHO reference centers. During fiscal year
13 2015, our network collected and analyzed a little over 30,000
14 samples, and provided about 500 samples to the gene bank.

15 This gives you some idea of where we are in the world.
16 The blue is where our partners are, and our sites. You'll see
17 some red dots. Those red dots represent our embassy
18 surveillance, which we are also involved with. And as you see,
19 it's over 30 countries and 400 sites.

20 I'm going to give you a little background on the
21 graphs here. Along the X axis, you will see the epi week.
22 Along the left-hand Y axis, you will see a number of specimens.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

88

1 The far right-hand side, you'll see the current influenza
2 season, and on the left-hand side, you'll see last year's
3 influenza season.

4 These data are for our military recruits. Military
5 recruits are particularly vulnerable to respiratory diseases.
6 Historically, up to 20 percent of recruit classes will be
7 hospitalized for respiratory illnesses. Obviously, that plays a
8 big role in progressing these individuals on to their next
9 assignment. So it's obviously a very important issue within the
10 military.

11 If you look at the right-hand side, you'll see that
12 this season has been very mild, very mild. You'll see a mix of
13 H1B and H3, but very low. What's more interesting, if you look
14 back into June, you'll see an outbreak of influenza B, which
15 highlights the need for year-round surveillance.

16 So again, these individuals are located at eight sites
17 throughout the United States. These data come from military
18 members and dependents located in the United States. Again, if
19 you look at the right-hand side, you'll see our current flu
20 situation, which is, again, is very mild compared to last year;
21 again, there's a mix of H1, H3, and influenza B.

22 And here's our data for Europe. These are military

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

89

1 members and their dependents: family members; wives, husbands,
2 children. And you see again very low levels, mostly H1, some
3 flu B as well. We have probably about 150,000 individuals that
4 come into this catchment area in Belgium, Germany, Italy,
5 Turkey, and the United Kingdom. So it's pretty widespread, but
6 again these surveillance data show that there's very little
7 influenza in our military populations.

8 This data is specific to Egypt. You might wonder why
9 do, we have slide specific to Egypt, where so far we've been
10 talking about regions. Egypt is a longstanding partner with the
11 DOD. We've had a laboratory there for over 50 years.

12 And aside from geopolitical reasons, Egypt is a very
13 important because in recent history, they have had a large
14 number of H5 cases reported, so we have a particular interest in
15 Egypt. Again, this is a fairly heavy flu season; it represents
16 a fairly heavy flu season. The vast majority of cases are H1,
17 very little flu B, and this really stands out, I think.

18 This slide represents both local and national
19 populations on their surveillance in Asia, and some of our
20 military members. We have military presence in Korea, in Japan,
21 in Guam, as well; other countries included in this, are the
22 Philippines, Thailand, and Cambodia, and Bhutan. So it is a

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

90

1 mix, really, of U.S. military and local and national
2 populations.

3 You can see, looking at the right hand side, this
4 season is a mix of H1, H3, and B, a little bit -- compared to
5 last year, a little bit stronger, a little bit heavier activity.
6 And if recent history is any indication, they may peak in a week
7 or two. Actually, over the past few years, we have seen that
8 peak in March/April in this particular region.

9 So in summary, North American, Europe military members
10 and dependents have experienced low flu activity so far.
11 Positive samples have been a mix H3 and H1. Globally, a mix of
12 H3 and H1, have been detected. In the DOD network, Egypt, so
13 far, has experienced a relatively heavy season dominated by H1,
14 and Asia has experienced a relatively heavy season with a mix of
15 circulated viruses.

16 Now, as I mentioned, I'm not going to go into great
17 detail regarding the phylogenic analyses. I would like to give
18 you some idea as to where the DOD sequences came from. You can
19 see, we submitted 196 sequences from a dozen countries and five
20 continents.

21 I'd like to just hit up some of the highlights of the
22 analysis: 66 percent of the total sequences were flu A,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

91

1 influenza A; 71 percent of those were (H1N1); 29 percent of the
2 flu As were (H3N2); 34 percent of the total sequences were
3 influenza B and 70 percent of those were Yamagata, and the rest
4 were Victoria; ninety-two influenza (H1N1) specimens were
5 successfully sequenced from 32 sites in 11 countries, and these
6 were collected between October 2015 and February 2016.

7 All 92 sequences classified as clade B, and 88 percent
8 of the sequences shared the newly-emerging mutations: S162N and
9 I216T. As for H3, 38 influenza specimens were successfully
10 sequenced from 13 sites in 7 countries, collected between August
11 2015 and February 2016; 84 percent of the H3 specimens
12 classified as clade 3C2A, containing the A/Hong Kong/4801/2014,
13 and 16 percent classified as the clade 3C3A, containing the
14 A/Switzerland/9715293/2013.

15 As I mentioned, to this point, the flu season has been
16 relatively mild. Most regions covered by the DOD influenza
17 surrounds network have seen very little activity. Overall, the
18 number of cases available for these vaccine effectiveness
19 analyses was down by over 90 percent from last year.

20 The midyear estimates are provided by our partners at
21 USAFSAM, Naval Health Research Center, and the Armed Forces
22 Health Surveillance Branch, Section Epi Analysis. Each was a

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

92

1 case-controlled study that used multi-variant logistic
2 progression to estimate the vaccine effectiveness; two of the
3 studies used control test negative method, that's the NHARC's
4 study and the USAFSAM study.

5 Epidemiology and analysis at the Armed Forces Health
6 Surveillance Branch used health controls. No analysis by flu
7 type, due to the small number of cases, and each influenza
8 infection were confirmed by PCR or viral culture.

9 Here, you see our testing criteria for ILI: if you
10 have a fever greater than 100.5 F, or 38 degrees C, and a cough
11 and/or sore throat; specimens should be collected within 72
12 hours of the onset of the symptoms.

13 And here is our USAFSAM. Thank you.

14 This is our USAFSAM estimate of vaccine effectiveness.
15 They adjusted for -- well, first off, the population they used
16 was health care beneficiaries, DOD health care beneficiaries,
17 but not active duty. So these are again, spouses and children
18 of active duty members.

19 The analysis is by a beneficiary group; children
20 versus adults, and vaccine type; inactivated vaccine versus the
21 live attenuated vaccine. In this analysis, test negative
22 controls were used and the models adjusted for age, gender, and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

93

1 region. Cases and controls were matched for week of illness, so
2 this is a conditional logistic regression.

3 There were 119 cases, 294 controls: 15 percent of the
4 cases and 37 percent of the controls were vaccinated; 53 percent
5 of all cases were (H1N1) so that's the dominant subtype; only 9
6 percent of the influenza A's were (H3N2) so we're not going to
7 be able to make comparisons between, or for each influenza
8 subgroup; and 38 percent of the cases were influenza B.

9 Of those vaccinated, 26 percent were vaccinated with
10 LAIV, the rest were vaccinated with the inactivated vaccine, so
11 it really impacts on our sub-analysis; so no analysis by flu
12 type and a limited analysis by vaccine type. Next slide,
13 please.

14 Here's our age distribution for the USAFSAM analysis.
15 You can see that about 50 percent of these individuals were
16 under the age of 18; 24 percent between 18 and 49, and 26
17 percent were 50-plus. Next slide, please. All right.

18 The overall estimate for vaccine effectiveness, for
19 all beneficiaries, that's adults and children combined, was
20 statistically significant and protective. The vaccine
21 effectiveness estimate for all beneficiaries, that's adults and
22 children combined, vaccinated with the inactivated virus

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

94

1 vaccine, was statistically significant and protective. Next
2 slide, please.

3 Here are our odds ratios. You can see for children at
4 the top of the table. You'll see vaccine effectiveness is 75
5 percent with a confidence interval of 43 to 89 percent. And
6 again, that's just comparing vaccinated to unvaccinated.

7 For adults, comparing vaccinated to unvaccinated, you
8 have a vaccine effectiveness of 64 percent. And when you try to
9 split out the inactivated versus the LAIV, you'll see that the
10 inactivated vaccine is quite high at 83 percent, and
11 statistically significant. The LAIV, you have very small
12 numbers, so the statistical power didn't make that comparison,
13 not very good. Next slide, please.

14 Next up, is our NHRC case control analysis. Next
15 slide please. Yep. Thank you. The population used in this
16 analysis, were civilians only. Some of them were DOD dependents
17 residing in Southern California or Illinois, and would have been
18 seen at outpatient clinics.

19 The civilians in this analysis, were completely
20 unassociated with the DOD, are individuals who sought healthcare
21 at the U.S./Mexico border. So again, these are all civilians;
22 part, are dependents, and these analyses adjusted for age, study

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

95

1 population, military dependents versus U.S./Mexico border
2 civilians, and month of illness. And there are 106 cases and
3 these were confirmed by PCR or viral culture.

4 Two hundred and sixty-seven controls and these are
5 again test negative controls. And you have, about 20 percent of
6 your cases were vaccinated and 38 percent of your controls; 58
7 percent of cases were (H1N3) and 25 percent were flu B with only
8 15 percent (H1N1).

9 So you can see how NHRC's data and analyses are almost
10 a mirror image of USAFSAM's. So it gives us an opportunity to
11 look at H3 or H1, but not together, not simultaneously, in a
12 logistic progression. Approximately 90 percent of the
13 vaccinated cases and controls were vaccinated with the
14 inactivated vaccine. So we're not seeing a lot of LAIV use in
15 our study populations.

16 Here's your age distribution: You can see 77 percent
17 are below the age of eighteen; about 20 percent 18 to 64, and 3
18 percent 65 and up. Overall, the adjusted VE was moderately
19 protective and statistically significant. For children, the VE
20 was moderately protective and statistically significant. The
21 adjusted VE for (H3N2) infection specifically, was moderately
22 protective and statistically significant.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

96

1 And here are the odds ratios: You can see the
2 overall, 48 percent; looking at H3, specifically, 66 percent
3 vaccine effectiveness, and children 18 and below, H3 only, you
4 see an odds ratio or I should say vaccine effectiveness of 66
5 percent.

6 The Armed Forces Health Surveillance Branch's analysis
7 used the health control, and the population analyzed here was
8 active component service members, and Navy, Air Force, Marines,
9 and Army. And these are both individuals residing within the
10 United States and outside the United States. We had 183 lab-
11 confirmed cases; last year, we had about 2,000 for this
12 analysis, to give you some idea.

13 Health controls were used. The medical encounters,
14 individuals who had medical encounters for injuries or mental
15 health conditions, with no ILI reported in any encounter, and no
16 medical encounters for influenza during the flu season. These
17 individual cases and controls were matched by sex, age, date,
18 and date of encounter and location.

19 In addition, the models adjusted for a five-year
20 vaccination status, meaning that if an individual had any flu
21 vaccination in the previous five years, they would be a yes; so
22 for any of it, whether it be five or just one. Overall and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

97

1 vaccine type VE were calculated.

2 In addition, going back to the five-year vaccination
3 status, that's proven to be a very important variable in our
4 models. About 90 percent of our cases and controls indicate a
5 vaccination in the previous five years. Here are our age
6 groups.

7 And I apologize. In your handout, I believe the last
8 age group was left off, but you can see the lion's share of our
9 cases, are between 30 and 39. Keep in mind that the U.S.
10 military, these are active duty individuals. The U.S. military
11 tends to be considerably younger and healthier than the
12 population at large.

13 So 84 percent of the cases were vaccinated and 87
14 percent of the controls; this obviously has a substantial impact
15 on statistical power; 90 percent of cases had prior flu vaccine
16 in the previous five years; of those vaccinated, 59 percent were
17 inactivated vaccine and 41 percent were vaccinated with the
18 LAIV.

19 Adjusted VE of 24 percent was calculated for overall,
20 and that was not statistically significant; adjusted VE of 16
21 percent for those who received the inactivated vaccine was
22 calculated, and that was not statistically significant; and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

98

1 adjusted VE of 39 percent was calculated for those who received
2 the LAIV; and again, not statistically significant.

3 Here are our odds ratios. So when looking at active
4 duty, there was no discernible vaccine effectiveness; however,
5 looking at the civilian populations, it was moderate to strong.

6 So summarizing the results: Regarding USAFSAM and
7 NHRC vaccine analysis, overall VE, all flu and vaccination types
8 were statistically significant and moderately protective; the
9 vaccine effectiveness for inactivated vaccine, specifically, was
10 statistically significant and moderately to highly protective.

11 The USAFSAM and NHR C analysis indicate that the
12 inactivated vaccine prevented between 64 and 83 percent of
13 medically-attended influenza cases. Regarding the Armed Forces
14 Health Surveillance Branch's analysis, none of the findings were
15 statistically significant, and there are substantial limitations
16 to our work here.

17 Subjects were sick enough to seek medical attention,
18 so we can't really comment on the impact for the less severe
19 cases. Due to relatively small numbers of cases, the vaccine
20 effectiveness by flu subtypes, or vaccine type could not be
21 estimated. For the USAFSAM and NHRC analysis, over 80 percent
22 of vaccinated cases and controls were vaccinated with the IIV,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

99

1 so you can't compare VE by vaccine subtype. And the numbers
2 were too small to adequately evaluate the LAIV vaccine.

3 Regarding the Armed Forces Health Surveillance Branch
4 analysis, the active duty military population is highly
5 immunized; generally speaking, it's over 90 percent, although,
6 this year it's a little bit lower at this point, due to some
7 delays in getting the vaccine out. This could have a negative
8 impact on the VE, potential methodological issues.

9 Keep in mind, if 87 percent of your controls are
10 vaccinated, your number requirement for statistical power
11 purposes is very high, and that is the case in our situation.
12 We have -- 87 percent of our controls were vaccinated. So you
13 have potential methodological issues, potential biological
14 effects, such as it's an attenuated immune response, which was
15 mentioned a little bit earlier today, with repeated exposures.

16 Also the military population is younger and healthier,
17 so we can't really comment on vaccine impact in older, high-risk
18 populations. And again, the small number of cases really
19 limited the analysis.

20 I'd like to acknowledge our partners, too many to
21 mention, but they had a lot of contributions to this work, and
22 we appreciate their efforts. And I'll be happy to take any

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

100

1 questions.

2 DR. LYNFIELD: Thank you very much, Captain Cooper.

3 Are there some clarifying questions?

4 **QUESTIONS**

5 Yes, Dr. Monto?

6 DR. MONTO: I think the results from the NHRC analysis
7 are particularly interesting. First of all, because you got a
8 fair number of (H3N2)'s and one of the sites was Illinois, and
9 the other was San Diego?

10 DR. COOPER: San Diego, yes. And I checked into this,
11 it's very -- less than 5 percent of the cases came from
12 Illinois.

13 DR. MONTO: Okay. All right.

14 DR. COOPER: So it's --

15 DR. MONTO: Because in the Midwest, it's been nearly
16 all pandemic/H1N1 --

17 DR. COOPER: Right.

18 DR. MONTO: -- with a smattering of B's from the start
19 of the year. Obviously, you don't know what clade this virus
20 belonged to, but the estimates are very high for (H3N2). Do you
21 have any information about past vaccination of these
22 individuals?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

101

1 DR. COOPER: No. These --

2 DR. MONTO: Not yet.

3 DR. COOPER: Well, exactly. These individuals, we
4 don't have access to their -- currently, to their medical files.

5 DR. MONTO: Um-hm.

6 DR. COOPER: So there's no information on previous
7 vaccine.

8 DR. MONTO: Um-hm. Thank you.

9 DR. LYNFIELD: So Captain Cooper, I wonder if I might
10 ask you a question.

11 DR. COOPER: Sure.

12 DR. LYNFIELD: You, I believe, you had mentioned that
13 there was some characterization of the B viruses, with 70
14 percent being of the Yamagata lineage and 3 percent Victoria.
15 I'm wondering if you can comment. Were these viruses that were
16 from around the world or were they from a particular region?

17 And what proportion of the -- what is the total number
18 of viruses that were characterized, compared with the total
19 number that you have reported?

20 DR. COOPER: Well, you've got to remember these
21 analyses are just a subset of what was already presented.

22 DR. LYNFIELD: Yeah.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

102

1 DR. COOPER: So I can tell you that 196 sequences came
2 from our network into the CDC analysis.

3 DR. LYNFIELD: Okay.

4 DR. COOPER: But the total number of viruses, I'm
5 afraid I don't have information on.

6 DR. LYNFIELD: Okay. And were these from throughout
7 your surveillance system, or were they from a particular area?

8 DR. COOPER: They're from throughout the surveillance
9 system, but I don't have information as to where exactly the B's
10 came from.

11 DR. LYNFIELD: Okay.

12 DR. COOPER: Yep.

13 DR. LYNFIELD: Thank you very much.

14 Any other questions?

15 (No response.)

16 DR. LYNFIELD: Okay. Thank you, Dr. Cooper. Okay.

17 And I would like to invite our next speaker, Dr.
18 Zhiping Ye, from the FDA, and Dr. Ye is a senior investigator at
19 the Division of Viral Products; Office of Vaccines Research and
20 Review, at CBER/FDA, and he will be speaking to us on vaccine
21 responses.

22 DR. YE: Thank you very much.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

103

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

VACCINE RESPONSES

DR. YE: In her presentation, Dr. Katz presented an antigenic characterization of the circulating virus using ferret model. In this presentation, I will present the antigenic characteristics of a circulating virus using human cell. And those serum panels usually come from the clinical trial, if the trivalent or quadrivalent vaccine contained the current vaccine compositions.

And different from the ferret study, in human, we do not have serum from the clinical trial contain the proposed antigens such as Hong Kong/4801. So in my presentation, I'm only looking at the antigenic relationships of a circulating virus, compared with reference virus, as usually it's the virus that are used for production of the vaccine.

And also, the sera panel usually come from the clinical trial, contains the current vaccines. And usually the panels contain 24 individual serums. So for a trivalent vaccine, we have five panels, and for a quadrivalent vaccine, we collected seven cell panels, and those panels were distributed to the six laboratories from WHO, CDC, ERL's.

And then the method is exactly the same as the method,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

104

1 which was mentioned by Dr. Katz, and we use HI assay, and also
2 we use microneutralization assays, and to increase the
3 sensitivity of the assay, the serum panel is pre-screened to
4 eliminate the low antibody. The samples contain a low antibody
5 titer to increase the sensitivity. So my presentation is just
6 going to focus on, to compare the antibody titer against the
7 circulating virus, versus the reference virus.

8 And we wanted to look at, whether the serum sample
9 come from a clinical trial cannot tell the difference between a
10 circulating virus and the reference virus. And if the
11 relationship of the circulating virus is very similar to the
12 reference virus, that means the antibody can cover pretty well,
13 to the circulating virus. And if we see the difference that
14 means the antigen similarly, the antibody may not cover very
15 well, to the circulating virus and that's indicate that this
16 strain probably will be updated. And the assays, we don't have
17 the sera from the clinical trial that contain the proposed
18 antigen, so only see the one way.

19 This slide shows the serum panels from trivalent
20 vaccine. I just wanted to point it to you that the vaccine
21 contains (H1N1). In this case, A/Christchurch is the
22 California-like virus.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

105

1 And in the first cell panels, we can see this is from
2 Australia. It contain the A/Christchurch for (H1N1); for (H3N2)
3 it's Switzerland and for B -- is a B/Phuket. And for China,
4 they use a different (H3N2), but it is still this Switzerland-
5 like virus.

6 And this slide shows the quadrivalent, and basically
7 it's similar to the trivalent. The only thing that's different
8 is it contained the B/Brisbane-like antigens in the clinical
9 trial. Okay. Now, I want to focus on (H1N1) virus.

10 And just to refresh your memory, the virus we selected
11 are from the start. So here is, as Dr. Katz mentioned, the
12 (H1N1) virus, the majority of them are clades 6B1 and 6B2. And
13 what we did is we choose the virus from those clades.

14 Okay. This slide just show to you that -- these our
15 reference antigens, either California or California-like; either
16 California, itself, or A/Christchurch. And for the
17 representative virus, which unlike the ferret study, for humans,
18 they're for human serology study we only can include a few
19 antigens. So we're not select all of them, just a few, to study
20 the antigenic differences.

21 And you can see here, we include 6B1. And also we
22 tried to cover the different geographic, from Michigan, from

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

106

1 Asia, and that also contained the 6B2 viruses. And then also,
2 we want to include some of the non 6B1 or 6B2 virus.

3 Okay. This slide shows the summary HI titers from six
4 lab, and then we look the antigenic, the differences of the
5 circulating viruses compared with the reference virus. The red
6 bar shows the summary HI, relative HI titers from adults. Then
7 the blue one, are from the old adults. Then the green one, are
8 from children.

9 By the way, the children come from the age 6 months to
10 3 years old, and for some panels, from the 6 to 2 years, and
11 some panel from 3 years, and 3 years comes from China. And then
12 for children, they immunize either one dose or two doses, based
13 upon the previous immunization history.

14 And here you can see that what we will try to compare
15 the circulating virus with reference virus. Since the vaccine
16 produced from the vaccine viruses are from egg, so here we
17 wanted to compare the antibody against eight propagated (H1N1)
18 virus.

19 And you can see here, that is the reference virus.
20 And then now, we look at the relative GMT titer compared to this
21 reference virus. First of all, you can see that the second
22 column, are the antibody against cell-propagated (H1N1) virus.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

107

1 And you can see here, this indicated that the antibody against
2 egg-propagated virus, different from cell-propagated virus, and
3 it's in the singular virus, but propagating a different host and
4 that indicate that maybe some of the antibody recognize egg, did
5 not recognize cell-based viruses.

6 And then the rest of them, I just wanted to show to
7 you our color-coded too. And the blue one 6B1 virus, I just
8 wanted you to see the difference. And then the green one, are
9 the 6B2 viruses.

10 We look at this, the relative to the compared to.
11 Usually we use a 50 percent, just to see if a -- I think some
12 study shows that if the antibody, the relative antibody above
13 the 50 percent, it most likely they simulate a good, or match
14 well to the reference virus. Anyway, so we -- just look at the
15 overall pattern.

16 And here, we include either egg isolates or cell
17 isolates. And overall you can see that either adult or
18 children, it's react relatively well to the 6B1 and 6B2 viruses.
19 However, when you -- next slide shows that when you compare the
20 antibody, against the cell-propagated virus, you can see the
21 different pattern.

22 Here you can see that when we use a cell-based virus

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

108

1 as a comparative, as a reference, you can see that the egg-based
2 virus have very -- again, you can see this -- they have a very
3 high antibody titer, compared with the cell-propagated virus.
4 And because you compare now is different, and the rest of the
5 virus you can see that when you compare with the cell-propagated
6 virus, the circulating virus are covered pretty well.

7 So this data shows that the majority of the
8 representative (H1N1) virus tested, react well with the human
9 serum collected from an individual who received the current
10 vaccine. And however some of the recent viruses, like 6B1 and
11 6B2 reacted poorly, but the majority react well.

12 Here is the point that we -- here is, just to address
13 your attention that we probably needed to follow up those
14 viruses, and see how those viruses evolved antigenically.

15 Now, we move our (H3N2). Again, we choose the viruses
16 contained 3C2A and 3C3A, but a majority is the 3C2A. And here
17 you can see that the majority of the virus are from 3C2A and
18 some of 3C3A, or 3C3B. And the underlying virus was used in
19 microneutralization assay.

20 As Dr. Katz mentioned, some of the virus does not
21 aggregate red blood cells, so you cannot do that in HI assay.
22 However, we include those viruses in microneutralization assay.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

109

1 Again, it's similar to the (H1N1) in here, we compare
2 the cell-propagated virus. And again, the blue bar indicating
3 the viruses belong to 3C2A, and the red represent the 3C3A
4 viruses. And as you can see here that the majority of the virus
5 reacted poorly, compared with the cell-propagated reference
6 virus.

7 Then regardless, cell or egg, so this -- yeah that is
8 -- okay, I think it's -- and also, similar to (H1N1), you can
9 see that when we compare with cell-propagated (H1N1), which is a
10 Switzerland virus, the Switzerland cell-propagated virus react
11 relatively low, compared with egg-propagated virus. And also,
12 you can see here that the majority of these viruses reacted
13 poorly, compared with the egg-propagated virus.

14 Now, if compared with cell-propagated virus, a cell-
15 propagated Switzerland, which is the current vaccine virus, then
16 you can see that the majority of the circulating virus that we
17 choose for this study, reacted well compared with those from the
18 data using egg-propagated virus. So that since we do not have
19 the serum from, like the Hong Kong/4801 virus, so we cannot see
20 how the same reacted to the circulating virus.

21 Okay. This slide show that the -- if we switch to
22 Hong Kong/4801 virus, could -- may increase the coverage of the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

110

1 vaccine, but however, we do not have the serum against this
2 virus, so this data only suggested that from the ferret study.
3 And again, the viruses were also used in microneutralization
4 assay. And here the similar pattern, but in a different degrees
5 that -- this one shows the egg-propagated virus.

6 You can see that the majority of the virus is not
7 covered well with this -- with the sera from these clinical
8 trial contain the Switzerland-like virus. However, when you
9 compare with the cell-propagated virus, now you can see the
10 coverage it's much better.

11 So the bottom line for the (H3N2) viruses, compared to
12 the HI titer against cell-propagated Switzerland vaccine virus,
13 the HI titer of the antibody against some of the represented
14 virus, was significantly reduced. When measured against a cell-
15 propagated virus, the GMT titer is higher, and also using
16 microneutralization assay, it confirm its finding.

17 Now, move on B viruses. This slide shows both
18 Victoria and Yamagata lineage virus, and as you can see here,
19 the B/Phuket is Yamagata reference virus, and B/Brisbane/60 is
20 the Victoria-like virus. And here you see that the green color-
21 coded are the viruses from Yamagata lineages, and the brown one
22 represents the viruses from the Victoria lineage.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

111

1 Here, I want you to pay attention that's because this
2 is -- these all come from the trivalent vaccine. And now, in
3 this study, we include the virus, the circulating virus from
4 Yamagata lineage and from Victoria lineage.

5 And without looking hard, you can see that Yamagata
6 virus, circulating virus, react relatively well to the reference
7 antigen, where the circulating virus, from Victoria lineage, you
8 can see this, it covered poorly, indicating that the vaccine
9 contained Phuket covered well to the virus, similar to the
10 Yamagata virus, because it does not contain antigen against the
11 Victoria, then it's Victoria virus does not cover well, and very
12 clear in this study.

13 This slide just shows conversely, this slide show the
14 reactivity using quadrivalent vaccine. And in this study, we
15 didn't include Yamagata virus. We just include the Victoria
16 virus that did not cover well in the previous slide.

17 And you can see here, majority of the virus covered
18 pretty well, using the -- compared with the even egg-propagated
19 Brisbane/60 virus. And for a B virus, a GMT of antibodies
20 against the majority of a recent B/Yamagata lineage virus was
21 similar to the HI titer, against Phuket vaccine virus.

22 As expected, the GMT titer to the Victoria lineage

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

112

1 virus was reduced in the panels that not contain this antigen.
2 Where the antigen -- where the panels contain both, covered both
3 well, to either Victoria or Yamagata viruses.

4 To wrap it up, the majority of the recent
5 representative viruses reacted well with the human sera
6 collected from an individual who received the vaccine contained
7 California/07-like antigens. Even though there are some viruses
8 -- some of the viruses not react well, but it does not change
9 the conclusion.

10 And for (H3N2) virus, GMT titer against (H3N2)
11 viruses, significantly reduced compared to the HI titer against
12 egg-propagated virus, which is Switzerland-like virus, but less
13 so when compared to the egg-propagated virus. And for B
14 viruses, it's pretty clear if the vaccine does not contain the
15 next -- the (inaudible) B, and does not cover well for both
16 lineages. Thank you.

17 DR. LYNFIELD: Thank you very much, Dr. Ye.

18 Does anyone have any clarifying questions? Dr. Monto?

19

20 **QUESTIONS**

21 DR. MONTO: I'm a little surprised, given the fact
22 that you gave egg-adapted virus in the vaccine that the response

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

113

1 is better to cell-culture-grown antigens.

2 DR. YE: I don't think the data shows the -- could you
3 point out exactly, which virus --

4 DR. MONTO: Well, I'm talking about the (H3N2). The
5 summary, is that the "measured against cell-cultured propagated
6 virus, GMT of antibodies against recent viruses was relatively
7 higher." Is that -- maybe I don't understand, which is -- are
8 you comparing in the HI test, with antigens that are cell-
9 culture-propagated versus egg-propagated?

10 DR. YE: I think when you compare with cell-propagated
11 virus, we are referring to the circulating virus, and the virus
12 not covered so well. However, when you compare with a cell-
13 propagated virus, because now you normalize the antibody,
14 against a cell-propagated virus, because cell-propagated virus
15 compared with an egg-propagated virus, have relatively lower HI
16 titers.

17 Now, because the HI titers lower, now you compare with
18 the -- the circulating virus with the cell one. Now you see
19 that virus covered well, when you compare with the cell-
20 propagated virus. Indicate that if you choose the virus, the
21 (H3N2) virus, that stimulant antibody covered relatively well,
22 compared with the cell-propagated virus. That virus may be

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

114

1 better to be included in the vaccine, such as Hong Kong for the
2 4801 virus.

3 Did I answer your question?

4 DR. MONTO: In part.

5 DR. YE: Okay. We can discuss later.

6 DR. MONTO: Let's take this offline.

7 DR. YE: Okay. Thank you.

8 DR. LYNFIELD: Any other clarifying questions?

9 DR. KATZ: Yes, I have one. Are these individual sera
10 or are they pooled?

11 DR. YE: These are the individual sera. As I said,
12 each panel contains 24 to 30 sera samples, and this study, a
13 summary of this individual one, and also include -- we started
14 it in different labs.

15 And then here, I showed -- acknowledge that the data
16 from what I presented, I'll summarize it from different, WHO and
17 ERL laboratories. And also I think for those who provided the
18 same sample for the study, a human sera sample now, is a very
19 (inaudible) especially when used for microneutralization assay,
20 we use a relatively large quantity.

21 DR. KATZ: Thank you.

22 DR. LYNFIELD: Thank you very much, Dr. Ye.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

115

1 Now, I would like to ask Dr. Manju Joshi to come to
2 the podium. And Dr. Joshi is the lead biologist at the Division
3 of Biological Standards and Quality Control, the Office of
4 Compliance and Biologics Quality at CBER/FDA. And she will be
5 speaking to us on candidate vaccine strains and potency
6 reagents. Dr. Joshi.

7 DR. JOSHI: I don't need this.

8
9 **CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS**

10 DR. JOSHI: Hello everybody. I work in Division of
11 Biological Standards and Quality Control, in the Office of
12 Compliance and Biological Quality at CBER. "DBSQC" as we
13 abbreviate our division. It's too long a name.

14 In collaboration with other essential regulatory
15 laboratories, participate in generation and calibration of
16 reagents required for testing of influenza vaccine. Our
17 division also manages and provides these reagents to all U.S.
18 licensed manufacturers.

19 In next 10 to 12 minutes, I will give you an update on
20 the candidate vaccine strains, and go over our division's goal
21 towards preparing and supplying influenza vaccine testing
22 reagents for 2016-2017 season.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

116

1 In my talk, I will go over currently-used vaccine
2 strains, and also the WHO recommendation for 2016-2017 seasonal
3 vaccines, both the trivalent and quadrivalent. I'll give you an
4 update on the available reagents for each of the strains, as we
5 have now.

6 And lastly, I'll make some general comments about use
7 of SRID reagents, and which I will tell, which is more for the
8 audience, the users of the reagent, not so much for the
9 Committee, as such.

10 Coming to the (H1N1) strain, for influenza A, (H1N1)
11 type the current vaccine strain was the A/California/7/2009-like
12 virus. A number of reassortants have been used in the
13 manufacture of vaccine last season. This included the X179A and
14 X181 reassortants, even the NIB-74 and 74-xp reassortants for
15 A/Christchurch, which is a California-like, have been used in
16 vaccine.

17 In addition, B/Brisbane/10/2010, which is also a
18 A/California/7-like virus, was used in vaccines. Most of us in
19 this audience know that WHO and they have been repeated by all
20 the previous speakers that the WHO has recommended there'd be no
21 change for (H1N1) strain for upcoming influenza season, and
22 A/California-like virus remains as the (H1N1) component.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

117

1 I've listed here, and I'm not going to go over the
2 names here, all the various candidate vaccine viruses which are
3 A/California-like. I just want to remind A/California/7/pdm09-
4 like virus has also been recommended for 2016 southern
5 hemisphere campaign. We all understand that inclusion of WHO-
6 proposed strains in the vaccine is based on approval by the
7 Committee today. To stop, and for now, just let's look at the
8 reagents that are currently available for testing the strain.

9 For homologous reference antigen for reassortant X179A
10 and X181 are available from CBER. In past, some of the vaccine
11 manufacturers have used a reference antigen from other ERL's
12 such as egg-derived antigen for X181 from TGA, NIB-74 from
13 NIBSC, as well as cell-derived reference antigen for
14 A/Brisbane/10 from NIBSC.

15 As far as available antisera are concerned, three
16 different antisera lots are available from CBER for testing of
17 (H1N1) component. We'd like to point out that we are getting
18 low on the two lots, 1404 and 1405 that most of the
19 manufacturers had used last season, but we have already prepared
20 a new lot for testing. And in addition, we are in process of
21 making additional lots in coming weeks.

22 At this point, again, I would like to remind the users

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

118

1 of the reagent that some manufacturers may choose to use
2 reagents prepared by other ERL's. CBER will authorize use of
3 those reagents on a case by case basis. We would like to know
4 ahead of time which reagent each of the manufacturers will be
5 using, and this is very important for us because this will help
6 us in planning for all the vaccine lot release activities.

7 Coming to the (H3N2) strain for 2015-2016 season, the
8 recommended strain was A/Switzerland/9715293/2013-like virus.
9 The NIB-88 reassortant of A/Switzerland, and IVR-175 reassortant
10 of A/South Australia were used for vaccine manufacturing. Wild
11 type A/South Australia was used in cell-derived vaccine.

12 Last year, the reagents were made available by ERL's.
13 NIB-88 reagent for egg-derived vaccine prepared using NIB-88
14 reassortants, CBER, and NIBSC, and NIID had provided the
15 reagents for IBR-75 egg-derived vaccines. TGA had prepared and
16 supplied the reagents, and as far as A/South Australia cell-
17 based products were concerned, reagents were provided both by
18 CBER and NIBSC.

19 The WHO has recommended a change of the strain, and
20 the recommendation is for A/Hong Kong/4801/2014-like virus. The
21 various candidate vaccine viruses in this group are listed here.
22 Let me just remind everybody, this has been recommended as the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

119

1 (H3N2) strain for 2016 southern hemisphere campaign as well.

2 CBER is in process of getting reagents ready for
3 A/Hong Kong, if the strain gets selected by the Committee, and
4 we are anticipating the target availability date for this
5 reagent to be late May into early June.

6 I just want to remind that the reagent for X-263B, the
7 reassortant of A/Hong Kong, is available from NIBSC. And
8 similarly, for X-257A reassortant of A/New Caledonia, which is
9 A/Hong Kong-like strain, are also available from TGA and NIBSC.
10 Again, I want to reiterate that CBER will authorize the use of
11 reagents from other ERL's on a case by case basis. Please
12 consult with DBSQC prior to using reagents from other ERL's.

13 Coming to the influenza B; for 2015-2016 season for
14 trivalent vaccine, the recommendation was to use the B/Phuket-
15 like virus from B/Yamagata lineage. Wild type B/Phuket and Wild
16 type B/Utah/09/2014, which is a Phuket-like virus, were used in
17 vaccine preparation last season. For egg-based product using
18 B/Phuket, reagents were prepared by CBER, NIBSC, and TGA. And
19 for cell-based product prepared using B/Utah, both CBER and
20 NIBSC had prepared reagents.

21 WHO has recommended a change for B strain in a
22 trivalent vaccine; for 2016-2017 influenza season, WHO

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

120

1 recommends that the trivalent vaccine contain a B/Brisbane/60-
2 like virus from B/Victoria lineage. The various candidate
3 vaccine viruses for these groups are, again, listed here on the
4 slide. Please note that the B/Brisbane/60 was included as a
5 second B strain for quadrivalent vaccine in the previous season.

6 Again, this has also been recommended as the B
7 component for the southern hemisphere vaccine. If the strain is
8 selected by the Committee, here is CBER status of the reagent
9 currently: B/Brisbane/60 reference antigen for both egg and
10 cell-derived product are available from CBER.

11 If manufacturers do choose to use B strain, other than
12 B/Brisbane/60, CBER will vote to generate homologous reference
13 antigen standard, and the target availability will be around
14 May/June 2016. I'm sorry for the typo. It's 2016.

15 Coming down to availability of the antisera, which is
16 always needed, the inventory for antisera lots serum, which were
17 supplied last year, and most of the manufacturers have used,
18 this is getting low. We have already prepared two new lots of
19 antiserum, and they are available.

20 And once again, I think it's becoming too repetitive
21 to say that, please consult with us before start to using
22 reagents from other ERL's.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

121

1 We all know that the quadrivalent vaccines are
2 supposed to contain an additional B strain from alternate B
3 lineage, referred to as second B strain. During 2015-2016
4 season, WHO had recommended that the second B strain for
5 quadrivalent vaccine be B/Brisbane/60-like virus from B/Victoria
6 lineage. This year WHO has recommended a change for the second
7 B strain and quadrivalent vaccine.

8 For 2016-2017 influenza season WHO recommends that the
9 quadrivalent vaccine contain a B/Phuket-like virus from
10 B/Yamagata lineage. Again, here's the list of various B/Phuket-
11 like candidate vaccine viruses on the slide. Just to come back,
12 this strain was recommended as a B strain for both trivalent and
13 quadrivalent last year.

14 So basically, it is, we had this as a main B up there
15 this year, it is only for quadrivalent. And again, to remind
16 this has also been, similar recommendation has been made for
17 2016 southern hemisphere campaign. Looking at the reagents that
18 are available for the second B strain, the reagents for egg-
19 derived B/Phuket is available from CBER. Similar reagents for
20 B/Phuket were provided last year, even by NIBSC and TGA.

21 In addition, NIBSC had last year prepared reagents for
22 B/Brisbane/9/2014, which is a B/Phuket-like virus, and they had

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

122

1 prepared it for the last season, and they have it. For cell-
2 derived product, we do have B/Utah reference antigen for B/Utah
3 prepared by CBER. And similar reagent is also available from
4 NIBSC.

5 Coming to the different antiserum lots that are
6 available from CBER, if the strain is selected and it needs to
7 be used, we have lots 1507 and 1508, which were prepared last
8 year. As we are getting low on our inventory for those lots, we
9 have already prepared two new lots of antisera. Again, the
10 standard reminder, please consult with us for any of the reagent
11 use from any other ERL.

12 Now lastly, I would like to make some comments, which
13 are more relevant, again, to the users of the SRID reagents.
14 CBER-authorized reagent should be used to test potency of
15 vaccine marketed in U.S. CBER collaborates with other ERL's in
16 calibration of reagents, and can authorize the use of those
17 reagents.

18 Please remember that users have to obtain this reagent
19 directly from the ERL's. To avoid discrepancies, CBER
20 recommends that to use the reference antigen and reference
21 antisera from same source, and not mix and match. Again, we do
22 recommend that the same reagent be it's desirable to use the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

123

1 same reagents for your monovalent vaccine for the formulations
2 and any other follow-up studies.

3 One more additional reminder is, especially for those
4 who are getting into making new products, is, please discuss
5 with CBER about use of reagents in early phase. Manufacturers
6 and CBER can work together, to ensure that required reagents are
7 available to test new products.

8 And lastly, I would like to point out that if you have
9 any inquiries regarding CBER, our reference standards, and
10 reagent availability, and shipping, please contact CBER
11 Standards at the email address provided. And also, do please,
12 do notify us if you have any problem with the reagents, and we
13 will be happy to discuss.

14 Lastly, in closing, I want to emphasis that we at CBER
15 are committed to make every effort to ensure that reagents
16 appropriate for all strains elected are made available in timely
17 manner. We believe that making the influenza vaccine available
18 in timely manner, and ensuring vaccine consistency is a
19 responsibility shared by all of us here, and we work together as
20 a team to achieve this goal. Thank you. I will take any
21 questions.

22 DR. LYNFIELD: Thank you very much, Dr. Joshi.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

124

1 Any clarifying questions?

2 (No response.)

3 DR. LYNFIELD: Okay. Thank you.

4 DR. JOSHI: Thank you.

5 DR. LYNFIELD: We are running a little bit late, but I
6 think we would like to have the next talk prior to lunch, and so
7 I'd like to invite Dr. Matthew Downham to the podium, to speak
8 from the manufacturers' perspective. Dr. Downham is the
9 Associate Director of Biopharmaceutical Development Research and
10 Development at AstraZeneca/MedImmune.

11 DR. DOWNHAM: Okay. Good morning, or maybe good
12 afternoon everybody.

13

14 **COMMENTS FROM MANUFACTURERS**

15 DR. DOWNHAM: I'd like to firstly, thank the
16 Committee, on behalf of the flu manufacturing community, for
17 this opportunity to present their influenza perspective, the
18 industry perspective. As indicated on the slide, this is
19 presented, together, from Sanofi Pasteur sequeres (ph) GSK
20 Protein Sciences. And the company I work for, of course,
21 AstraZeneca/MedImmune.

22 So firstly, I'd like to start with where Sam Lee took

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

125

1 us last year at this time, and that is to reference the
2 complexity and intricate detail that's required for annual
3 influenza vaccine U.S. supply. And particularly also the
4 timeline, drawing attention to the strain selection decisions
5 that come at the end of February, and the limited timescale
6 taking approximately 6 months through to delivery and supply of
7 shipments.

8 So the point to make here is that any sort of delay in
9 the strain selection will impact vaccine distribution schedules
10 and that's indicated by the animation that we have on the slide
11 here. By clicking the button, you can see what happens if we
12 shift the strain selection even by a small period of time, to
13 the mid-to-late end of March. Okay.

14 So if you look at the U.S. influenza vaccine
15 distribution from 1980 through to the modern day, 2016, it's
16 quite an impressive statistic. If you look at the figure on the
17 left-hand side, 1980 to 2014, there's been a progressive
18 increase in the number of vaccines supplied to the U.S. markets.
19 In fact, the note's rather small, but up there, (inaudible) was
20 146,000,000/147,000,000 doses per year.

21 If you look at the figure on the right-hand side, you
22 can see the projection of how those supplies are delivered, at

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

126

1 least for the 2014-2015 season, with the first deliveries
2 implemented in September of that year, and then hitting the
3 approximate plateau, around 140,000,000 doses in about towards
4 the end of November of that same year. So, vaccine supply
5 obviously requires a well-matched strain, sufficient quantities,
6 and timely pre-season delivery, obviously all very important
7 factors.

8 And by checking the CDC website, I did prior to
9 submitting the slides, to date, as of the 19th of February,
10 2016, there's 146,000,000 doses, slightly over, distributed.
11 And those distributions and supply were initiated in early
12 September 2016. So if we think again, back to the, what if you
13 delay or what if we delay strain selection, how might that
14 impact things.

15 Well, in the 2014-2015 season strain selection was
16 implemented, not at the end of February; however, if we did it
17 at the end of March, the strain selection would have delayed the
18 initial dose supply, to approximately October 2014, and with a
19 commensurate meeting of the peak, not in late November 2014, but
20 actually late December, so quite a substantial shift.

21 This slide just briefly indicates to you how we are
22 faring for the current season. It indicates the influenza

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

127

1 strains that have been evaluated thus far for the northern
2 hemisphere. And we've heard already today, from several
3 presenters on the strains that were recommended last week, by
4 the WHO for the northern hemisphere.

5 What you can see is just the range, a number of
6 strains that have been evaluated by industry, and by other
7 organizations; for example, Doris Bucher's lab in New York
8 Medical College. And Doris is here today, as well.

9 What I'd like to also draw your attention to, is the
10 recent addition of the 6B1 and 6B2 strains, into the (H1N1)
11 portfolio, as a result of the strains that are emerging that Dr.
12 Katz demonstrated for us a little earlier today. So if you
13 think about these 6B strains that are emerging, manufacturers
14 have had some discussions regarding these, in terms of what
15 might be the impact for supply for the current season, and there
16 are some concerns regarding the late emerging (H1N1) genetic
17 subgroups.

18 Firstly, the (H1N1) viruses are typically a lower
19 yielding strain than the (H3N2) viruses, and so require longer
20 manufacturing campaigns to fulfill stock requirements.
21 Currently, as far as I'm aware, there are no new representative
22 viruses or CVV's confirmed, so that's Canada Vaccine Viruses

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

128

1 confirmed. To confirm, we would need, not just antigenicity,
2 data, and the selected candidate, obviously, but high growth
3 reassortants identified and also obviously, a potency assay
4 available as well.

5 As was mentioned a little earlier, manufacturers do
6 actually begin production of their flu vaccine candidates at
7 risk. And as is often the way, significant quantities of (H1N1)
8 amounts of 2016 have already been stockpiled. And delaying
9 further will impact timing and quantity of supply, accordingly.

10 So if we go back to the Visio gram that I showed a
11 little earlier, if we impact that scenario onto the current
12 status, a two to three week delay of (H1N1) strain selection
13 now, today, would delay influenza vaccine supply by
14 approximately four months.

15 So if we assume a two to three week delay to identify
16 representative viruses and confirm those, an additional three-
17 plus weeks to prepare the reassortants, and an additional
18 twelve-plus weeks to prepare potency assay reagents that shifts
19 the whole picture to the right-hand side, as you can see, and
20 obviously delays quite significantly, vaccine supply to the
21 market.

22 Moving on to how industry engages with multiple

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

129

1 stakeholders. So we don't just discuss amongst ourselves, we
2 engage very much with key stakeholders globally, with the WHO,
3 and also with HHS just to improve the season influenza vaccine
4 supply. And this Visio just gives you an idea of how many
5 meetings and what we've talked about, between today, the VRBPAC
6 meeting today, and last year's VRBPAC meeting, which was
7 actually on the fourth of March 2015.

8 In light blue, you can see the seasonal flu review
9 meetings. And these are the meetings that the likes of Dr.
10 Katz, etc., present from the WHO on the seasonal circulating
11 surveillance, from the GISRS that was mentioned a little
12 earlier, and (inaudible) were the manufacturers understand how
13 to improve their influenza vaccine supply support requirements
14 and mitigate risk from supply as well.

15 In green, you can see some additional meetings that
16 have been held through the year since the last VRBPAC meeting;
17 particularly, the two HHS meetings there. The influenza vaccine
18 virus mismatch and seasonal influenza vaccine improvements
19 exercise that then fed into the WHO meeting in Hong Kong towards
20 the end of November. And these were particularly with respect
21 to thinking about the response to strategies to supply late or
22 mismatched strains.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

130

1 And this was particularly built across from the (H3N2)
2 drift that occurred with the 2014-2015 season, but also we work
3 within that environment to discuss things like the pandemic
4 response, which is the meeting you can see here, on the corner
5 between the June and July of 2015. And throughout these
6 sessions, there's also been reference to assessing seasonal
7 vaccine supply, an impact to the adherence to the Nagoya
8 Protocol, which I'll briefly reference in a moment.

9 So how does it fit, in terms of seasonal influenza
10 vaccine improvement? Well, from the meetings that we had with
11 HHS, these were hosted June and November 2015, and had
12 representation from HHS, FDA, CDC, NIBS, and the industrial
13 parties, where we discussed a range of matters related to
14 surveillance characterization of vaccine improvements and supply
15 mitigation options. And these were pitched alongside a couple
16 of scenarios.

17 Scenarios based on well, what if there was a delay in
18 vaccine strain selection, through to April, what that might
19 mean, in terms of delays of vaccine availability, and impact on
20 immunization programs and schedules. What if then we had a
21 delay through to July, in that situation, manufacturing would be
22 well in process by then.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

131

1 It might require potentially two different vaccines in
2 the same campaign, and reduce uptake of late vaccine as a
3 consequence. So that's quite an extreme situation, so in the
4 rare circumstances of a late emerging strain, delaying selection
5 to mid-late March. That might be considered acceptable if there
6 are appropriate Canada vaccine viruses available, if the assay
7 reagents are in process and the state of development.

8 And then the further rare circumstance of a
9 significant delay, i.e., to beyond the April timescale, then
10 this will need to be centrally coordinated. And if you think
11 back to the 2009 (H1N1) pandemic, the kind of coordination, and
12 the tightness of response then, was considered the requirement
13 in that scenario for seasonal vaccine provision. So underlying
14 this, they're given multiple challenges the preference is for no
15 strain selection delay, at least from the manufacturers'
16 identification to date.

17 A brief few words about Nagoya: Nagoya features, in
18 the majority of the meetings, I referenced a little earlier, on
19 that spreadsheet between the two VRBPAC meetings. It was
20 developed from access and benefit sharing discussions at the
21 convention of biodiversity 2010, and came into force in October
22 2014. And this describes access to genetic resources and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

132

1 related traditional knowledge for potential research and
2 utilization purposes.

3 And this is whereby users on providers in genetic
4 resources and related traditional knowledge agree on a fair and
5 equitable sharing of benefits arising from their utilization.
6 You may be wondering why I'm mentioning this now. And that's
7 because there is the potential impact to seasonal influenza
8 strain availability as pathogens are included under the Nagoya
9 protocol.

10 In other words, under the obligations of the Nagoya
11 protocol, there will be the requirements negotiate terms of
12 pathogen use, and that may currently include seasonal
13 influenzas. So the bottom line there is that there is an
14 unknown impact of influenza vaccine availability, for the U.S.
15 market. However, the expectation is that there would be a delay
16 of some manner or form, while those obligations, those
17 negotiations were discussed and taken through.

18 So to conclude and allow us all to go for lunch;
19 concluding comments. It's important then, that timely vaccine
20 supply requires close collaboration and not just amongst the
21 manufacturers, but amongst the global stakeholders. And
22 communication is key as well, to ensure sufficient provision of

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

133

1 well-matched vaccine, and understanding of the strains, and
2 understanding of the critical reagents, as we've just heard as
3 well.

4 Timely strain selection ensures vaccine availability
5 and use, and the preferences for current strain recommendation
6 timelines. And if a change is required, do so for one strain by
7 mid-to-late March. The impact of adherence to Nagoya protocol
8 may be a delay in season influenza vaccine supply and
9 distribution in the U.S.

10 So there are ongoing discussions with regards to that,
11 as well, and the potential impacts, not just for the U.S., but
12 globally. So with that, I'd like to say thank you very much for
13 your attention, and I'll try to address any questions if
14 possible.

15 DR. LYNFIELD: Are there any clarifying questions?
16 Yes?

17 DR. WHARTON: Thank you. Given the mention of the
18 Nagoya Protocol, I wonder if someone could provide just a little
19 bit more information about, practically speaking, what we're
20 anticipating might happen. I would expect there wouldn't be any
21 impact on you, the inclusion of U.S. derived strains into
22 anything, but just wonder, from those who are more familiar with

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

134

1 all this than I am, practically speaking, what we might be
2 talking about here.

3 Dr. Katz?

4 DR. KATZ: Yes. It's a good thing. Thank you for
5 raising this, Dr. Downham.

6 So many countries have signed onto the Nagoya Treaty,
7 and this requires legislation in the country, in terms of how
8 they will or will not share viruses. The first point to make is
9 that the U.S. is not a signatory, so we cannot directly
10 influence how Nagoya will play out. And I'm sure Dr. Gellin has
11 been, also engaged in a lot of these discussions, but just to
12 give you from the U.S. CDC perspective, and from a WHO
13 Collaborating Center, what it could potentially mean to us.

14 Unless there is some global understanding of how
15 countries can receive benefit sharing, which is a mandate of
16 this protocol, we may be in a situation where CDC Collaborating
17 Center is not able to receive viruses from countries that have
18 signed on to Nagoya. This could also include other WHO
19 Collaborating Centers, like Australia and London. So it could
20 even restrict us sharing reference viruses between collaborating
21 centers.

22 This is -- I mean we're very, very concerned about

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

135

1 this. It has -- nothing has happened yet, but it's only been
2 just from the last, I believe from October, where it's really
3 coming to law that the countries that have signed on, are now
4 figuring out a way how to legislate this process. The other
5 difficulty is that this was a treaty that was negotiated through
6 international parties, mostly from ministries of the
7 environment.

8 So in many situations, we think even that the
9 ministries of health in different countries aren't really aware
10 yet of the true impact that this could have. Recently, the most
11 recent information that I have, is that certain countries -- so
12 countries who have signed on, and an example is the Netherlands,
13 they can make a statement that they freely, you know they give
14 up their rights to benefits. They just want to share their
15 viruses openly.

16 And this has been the basis. I mean this free sharing
17 has been the basis of this global influence and network and
18 vaccine virus selection for many years now. So countries can
19 choose to do that, but we know certain countries, developing
20 countries may not choose to do that, and really want to receive
21 some sort of benefit.

22 And then it, there's a requirement between the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

136

1 countries that are receiving the viruses, and potentially using
2 them for vaccine virus purposes that then there's some agreement
3 between the originating country. And I think that's what Dr.
4 Downham is talking about.

5 The manufactures are concerned that if we choose a
6 strain from a country that is requesting, sort of has signed
7 onto Nagoya, and is requesting benefit sharing, then there is an
8 agreement that has to occur, which could take many, many months.

9 And we know the timing of flu vaccines and that's not
10 going to really allow us to freely use vaccine viruses for
11 vaccine purposes from certain countries. That's the concern.
12 So some countries, I believe it's the UK, the Netherlands, and
13 I'm not sure; there's a third country, have approached WHO, and
14 have approached the director general, to really make this a
15 priority, and are trying to empower WHO to address this
16 specifically for influenza.

17 But you can imagine that it also, since all pathogens
18 technically fall under this Nagoya Protocol, it could affect
19 many other pathogens of public health significance. Do you want
20 to say anything?

21 DR. GELLIN: That was a great summary. Actually, what
22 I was going to say is that Ruth introduced this section. We'll

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

137

1 have Matthew talk before lunch.

2 UNIDENTIFIED PERSON: Sorry.

3 DR. GELLIN: And this is a huge topic, and Jackie did
4 a great job of summarizing it, and it's a conversation that many
5 of us had with the flu vaccine manufacturers because they saw
6 the potential here, given the tight timelines and the principal
7 of sharing strains from many places, and those strains that then
8 get shared on. So it further constrains a collaborating center
9 from receiving those strains, and their ability to move things
10 forward.

11 It is a big issue for which seasonal flu is, maybe the
12 test case. But as Jackie said at the executive board, the UK
13 brought this to the attention of Margaret Chan, and WHO is now
14 going to take a look at this because if I understand it
15 correctly, the only pathogen for which there is an agreement, an
16 international agreement on this, is pandemic influenza.

17 Everything else, seasonal influenza, other viruses,
18 other bacteria, and of particular interest to the UK was
19 implications on antimicrobial resistance, and the sharing of
20 those strains is what raised that issue to WHO, to take a look
21 at this and try to figure out a path forward, so that this
22 didn't become too cumbersome.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

138

1 DR. LYNFIELD: Well, thank you for raising it, and for
2 the discussion.

3 Dr. Monto?

4 DR. MONTO: How does the PIP Framework relate to this,
5 the pandemic influenza?

6 DR. KATZ: Right. So the PIP Framework was --

7 UNIDENTIFIED PERSON: Not before dinner, now.

8 (Laughter.)

9 DR. KATZ: -- was specifically crafted to exclude
10 seasonal influenza viruses, so it does not include seasonal
11 influenza, so we can't at this point, use the PIP Framework as a
12 demonstration of benefit sharing, for seasonal influenza
13 viruses. At this point in time, but there is some discussion as
14 to whether we just expand that, but it's going to take some
15 time. It's complicated.

16 DR. GELLIN: But the same general is that if pathogens
17 are to be shared, then there's some sharing of benefits, which
18 is a whole range of things from co-authorship, to access to
19 vaccines, and a number of different things, which is the larger
20 construct.

21 DR. LYNFIELD: Thank you.

22 Dr. Moore?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

139

1 DR. MOORE: Yeah, just a quick question. If we were
2 to not accept the WHO recommendation for the (H3N2) antigen, and
3 use last year's antigen, Switzerland, again this year, would
4 that actually delay that manufacturer, or would it have no
5 impact at all on the manufacturer -- on the timeline?

6 DR. DOWNHAM: It would potentially impact, as
7 manufacturers would start to prepare the Switzerland stockpile,
8 or reinstate the (H3N2) stockpile. So I believe, and I can't
9 speak for all manufacturers, certain organizations have already
10 started to stockpile the (H3N2) component, based on some of the
11 surveillance, some of the meetings, some of the intelligence
12 that's been gathered to date, in collaboration with the likes of
13 the WHO, etc. So potentially, it would represent a delay in the
14 event if the Switzerland was chosen.

15 DR. GELLIN: Matthew, if I can get you to comment on a
16 few things? So I appreciated your animated graphic that ran off
17 the page.

18 (Laughter.)

19 But I guess the question is, when it runs off the
20 page, because all the other boxes stay the same size, and I'm
21 curious about where industry is as far as, and maybe this is a
22 question also for FDA, but what's happening now, as far as doing

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

140

1 the things that are in those boxes, in less time?

2 For example, production would be shortened if yield
3 were better, and so, maybe if you could give us a global sense
4 of how technology, and some of the investments that are made in
5 pandemic preparedness might shorten those timelines so that it
6 doesn't, ultimately run off the page.

7 DR. DOWNHAM: Yeah. So some of the discussions we've
8 had, through the meeting schedule I showed earlier, have touched
9 on the means of improving technology, improving analytical
10 methods, applying new technologies, reverse genetics, etc.,
11 improving use of antibody reagents and so on. So there has
12 been, or there is, an ongoing series of discussions to improve
13 and maximize production and analytical capabilities.

14 And as I understand, from the meetings that we had
15 with the HHS during November last year, there's a hit list of
16 about 30 or 35 actions that are going to be worked through,
17 addressing how to improve and then be more expeditious in
18 manufacturing analysis.

19 DR. GELLIN: If I could make one other comment? That
20 in this, and I'm glad that you introduced this, but in these
21 table top exercises where we took a look at this to see how much
22 of a delay of a newly emerging strain, how long you could wait

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

141

1 to finish the cascade, because clearly you could make the
2 vaccine, but it would push things on.

3 And what was striking was the recognition that the
4 international interlocking of this system, that these
5 manufacturers are producing vaccine for many countries, and how
6 at the far end of it, the vaccination, and many countries don't
7 have much flexibility in altering the programs. I mean ours is,
8 to some degree, as well, but some were much more rigid, as far
9 as how a delay would make it much, much more difficult for them
10 to mount a vaccination program, which highlights the global
11 nature that's not just from the strains, but also on the
12 relatively few manufacturers supplying so many countries.

13 DR. LYNFIELD: Okay. It is time for lunch. We are
14 running a little bit behind and I suspect we will want to engage
15 in discussion, so I'm going to ask people to come back at one
16 o'clock sharp. I'm sorry that we are shortening lunch a bit,
17 but I think we do need to do this.

18 We also have public comment scheduled, so we can't be
19 too late for that. I also want to remind the Committee that we
20 are not able to discuss the topics that we have been talking
21 about today, because it is an open public meeting. So any
22 conversation related to the work that we are doing today, needs

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

142

1 to be held until we return as a committee.

2 Dr. Vijh, do you have anything to add?

3 DR. VIJH: No. I think that's good. You're good.

4 Yeah. Thank you.

5 Oh, that. Now that you ask, the Committee members
6 should please go to the room in the back because the lunch is
7 going to be brought there. So you don't have to go pick up your
8 box lunches, but please head back to the room.

9 LUNCH

10 DR. LYNFIELD: Okay. I'm going to ask members of the
11 Committee to please take their seats.

12 (Pause.)

13

14 **OPEN PUBLIC HEARING ANNOUNCEMENT**

15 DR. LYNFIELD: Okay. Now, we have gotten to the open
16 public hearing portion of the agenda, and so I am going to read
17 this statement:

18 "Open public hearing announcement for particular
19 matters involving specific parties meeting, e.g., product
20 specific.

21 Both the Food and Drug Administration (FDA) and the
22 public, believe in a transparent process for information

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

143

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

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

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

18

19 **OPEN PUBLIC HEARING**

20 DR. LYNFIELD: And so at this point, we do have two
21 individuals, who would like to make a statement. And we will
22 listen to the statement, however, we will not respond to the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

144

1 statement. So our first public speaker is Doris Boucher, from
2 NYMC.

3 DR. Vijn: She said she doesn't want to (inaudible).

4 MS. BOUCHER: (inaudible)

5 DR. LYNFIELD: Oh. Okay. Then we have one public
6 speaker. Thank you very much. This is Margaret Dayhoff-
7 Brannigan; Dr. Margaret Dayhoff-Brannigan, from NCHR.

8 DR. DAYHOFF-BRANNIGAN: Hi. My name is Dr. Margaret
9 Dayhoff-Brannigan. I'm the Patient Network Project Manager at
10 the National Center for Health Research. Our research center
11 scrutinizes scientific and medical data and provides objective
12 health information to patients, providers, and policy makers. We
13 do not accept funding from pharmaceutical companies and
14 therefore, I have no conflicts of interest.

15 Thank you very much for the opportunity to speak here
16 today. I completed my PhD in biochemistry and molecular biology
17 at the Johns Hopkins School of Public Health. I bring a
18 perspective as both a researcher and an advocate for public
19 health safety here today. I'm here today to express our very
20 strong concerns about the contradictory statements in evidence
21 regarding flu vaccines and antiviral medications from two
22 federal public health agencies: The FDA and the CDC.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

145

1 Patients and physicians are not well served when the
2 CDC seems to be promoting medical products, rather than
3 providing facts made available by FDA analysis. An effective
4 flu vaccine is critical for public health. The 2014-2015
5 vaccine had only a 23 percent efficacy, while this year's
6 vaccine efficacy was an improvement, it's important that we
7 implement strategies to improve the consistent efficacy of the
8 influenza vaccine.

9 When the vaccine does not work well, people think they
10 should not bother to get it. This is bad for both
11 pharmaceutical companies, who have unused doses of vaccine, and
12 for the general public that's less protected. We applaud the
13 FDA and CDC for changing the recommendations for children, to
14 reflect the poor efficacy of the live attenuated influenza
15 vaccine or nasal spray.

16 We hope the FDA will continue to look carefully at
17 whether the Agency should rescind approval for the flu nasal
18 spray, if it continues to show significantly lower efficacy than
19 the standard flu shots toward certain flu strains. There's
20 another problem, however, that I want to talk about today.

21 The CDC has strongly encouraged patients to use
22 antiviral medications if they get the flu. However, evidence

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

146

1 shows how little benefit Tamiflu offers, as well as significant
2 risks for children. Tamiflu must be taken within 48 hours of
3 symptoms to be effective, and even then, it will only help you
4 get better one day sooner.

5 That would be acceptable if Tamiflu was inexpensive
6 and had no risks, however Tamiflu is very expensive for many
7 people, and does have risks. Patients deserve unbiased
8 information about the risks and benefits, but CDC is providing
9 biased information. It exaggerates the benefits and minimizes
10 the risk.

11 The CDC's oddly promotional behavior regarding Tamiflu
12 seemed strange to us, until we read in the *BMJ* that the CDC
13 Foundation is accepting directed contributions from Roche, the
14 makers of Tamiflu. These contributions are then provided to the
15 CDC, creating a clear conflict of interest. Millions of
16 Americans count on the CDC to make health recommendations and
17 they depend on them to conduct research impartially.

18 The CDC has been strongly recommending Tamiflu,
19 despite controversy over its effectiveness. The FDA and CDC
20 present conflicting information about the efficacy of Tamiflu in
21 high risk populations. Tamiflu labels provide FDA-approved
22 information that is starkly different from what is recommended

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

147

1 by the CDC.

2 The FDA states that "Tamiflu has not been tested in
3 patients with chronic cardiac disease, or respiratory disease."
4 However, the CDC provides an informational handout that states,
5 in bold, that "if you have a chronic illness, such as asthma or
6 chronic heart disease, antiviral drugs can mean the difference
7 between a mild illness and a hospital stay." There is no
8 evidence to back up that statement.

9 Thank you very much for your time.

10 DR. LYNFIELD: Thank you. Okay. I don't think we
11 have any additional public speakers, so at this point, we are
12 now moving to discussion. And what I would like to do is open
13 the floor for discussion. I know that we've had some initial
14 clarifying questions and conversation this morning, but why
15 don't I first open up and see if anyone has any issues to bring
16 up.

17

18 **COMMITTEE DISCUSSION**

19 DR. LYNFIELD: Dr. Sawyer?

20 DR. COOPER: Oh, I'm sorry.

21 DR. LYNFIELD: I'm sorry.

22 DR. COOPER: Perfect timing.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

148

1 DR. SAWYER: You can go first.

2 DR. LYNFIELD: Okay. Dr. Sawyer is yielding to Dr.
3 Cooper.

4 DR. COOPER: We'll be here all day. I just want to
5 clear up your question regarding where the B/Yamagata viruses in
6 our analysis came from. It turns out they came from throughout
7 our network: Egypt, Germany, Washington State, California. And
8 the B/Victoria also comes from a variety of places: Japan,
9 Egypt, and Washington State, as well.

10 I'd like to thank my colleagues USAFSAM, who furnished
11 me with this information. They attend this meeting every year.
12 So thanks.

13 DR. LYNFIELD: Thank you very much, Captain Cooper.
14 That actually does remind me. We had a couple of questions for
15 Dr. Grohskopf from this morning. Lisa, did you get a chance to
16 --

17 DR. GROHSKOPF: Yes.

18 DR. LYNFIELD: -- take a look?

19 DR. GROHSKOPF: Yes. I got some additional
20 information. With regard to the second question, which had to
21 do with whether or not we had anything else we could say about
22 the (H3N2) isolates, in cases, in the U.S. Flu VE Network data.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

149

1 The investigators feel that they're really isn't
2 enough to draw any conclusions, however the VE for all A, all
3 influenza A, is very similar to the VE when the (H1N1) isolates
4 are pulled out, if that's helpful. But I can't get any specific
5 information about those cases, aside from that.

6 With regard to the earlier question, which had to do
7 with, in the, I think it's the third slide, which was the slide
8 that depicted the virologic surveillance results from the Public
9 Health Laboratories, that is submitted to the CDC on a weekly
10 basis.

11 The question was, I believe, "What proportion of the
12 influenza B isolates, were not subtyped?"

13 And in what I have here is actually that same
14 information for week eight, because the slides were only just
15 updated within the last hour or so, but the numbers are not very
16 different, I would gather, from the week seven data. Among the
17 influenza B isolates, just for week eight, the most recent week
18 we have data, 56.4 percent were not sub-lineaged. Lineage
19 testing was not performed. And among all of those cumulatively,
20 since October 4, 2015, lineage testing was not performed for
21 45.7 percent.

22 DR. LYNFIELD: Okay. Thank you very much. I really

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

150

1 appreciate your checking that.

2 DR. GROHSKOPF: You're welcome.

3 DR. LYNFIELD: Dr. Sawyer?

4 DR. SAWYER: Yeah. My question relates to this
5 influenza B sub-lineage topic. And as not a long-term flu
6 watcher, I'm interested in the perspective of those who have
7 seen the B strains come and go. Dr. Katz made the point that
8 they tend to cycle every few years. I'm wondering how regular
9 that is and how often, if you can tell me, it started to look
10 like it was coming, and then didn't come because again, like
11 many of the comments earlier this morning, it seems to be pretty
12 close to make this call between Yamagata and Victoria.

13 DR. KATZ: Yeah. I don't have the historical
14 knowledge that my predecessor had, I'm afraid, but I do know
15 that the lineages do cycle. I can't say that there's
16 predictability, that there's a predictable pattern every two
17 years or three years. I can't say that.

18 All I can say, I think, is what I said this morning,
19 is that we know this shift from one lineage to the other happens
20 with some regularity. It may not be every -- or it continues to
21 happen. Maybe that's a better term to turn a phrase.

22 And just from the available data that we have seen

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

151

1 globally since, I would say, August, sort of the end of the
2 southern hemisphere season, there certainly seems to be that
3 shift that is happening at this time. Whether that will happen,
4 and it will -- B/Victoria will predominate in the U.S. next
5 season, I can't tell you that.

6 DR. LYNFIELD: Dr. Moore?

7 DR. MOORE: Yeah. I'm a little bit concerned -- not
8 concerned. At least I'd like someone who knows more about flu,
9 which is most of the people here at this table, than I do, to
10 explain to me why, or at least convince me, as to the (H3N2)
11 antigen change that we're making. What is really to be gained
12 by that?

13 And especially in light of the fact that the year
14 before this year, we had a pretty bad epidemic of flu, from
15 (H3N2), guessing wrong on that antigen strain. And then we,
16 this year, either we have exhaustion susceptibles, or effective
17 vaccine coverage. And it seems to be working. So I want to
18 know why we want to change.

19 DR. KATZ: Okay. Just to address the last question.
20 I think H3 is, globally on the downturn this year. It was a lot
21 of (H3N2) in the previous couple of seasons and that maybe
22 because so it may mean that the immunity, it has built up

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

152

1 naturally, as well as, through vaccination.

2 I mean there are many parts of the world that don't
3 vaccinate a large portion of their population. And I would say,
4 overall, we've seen a very modest (H3N2) season this year
5 globally. To speak to the WHO recommendation to move to the
6 Hong Kong/4801, and this is sort of data that we've gathered, I
7 mean this decision was first made in September last year, for
8 the southern hemisphere, and there was always some concern that
9 because the 3C2A genetic group was predominant, we believe that
10 that is the virus that we need to follow most closely, and
11 track.

12 It does look like the 3C3A viruses -- although there's
13 been some modest activity in Europe -- they are not the
14 predominant. They haven't been the predominant strain, at all,
15 since these viruses emerged, or since these viruses took off.
16 And the earlier decision to go with Switzerland was, there was
17 more 3C3A at that time, but it was largely based on the
18 availability of the Switzerland vaccine component, a candidate
19 vaccine virus.

20 This time last year, we knew the 3C2A viruses were
21 beginning to predominate, but there was very limited data, and
22 not enough information on candidate vaccine viruses. So these

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

153

1 are the egg-grown viruses. We didn't understand the properties
2 of the 3C2A viruses well enough, and so the decision in February
3 of last year, for the WHO, was just go with Switzerland.

4 Between February and September of last year, there
5 were many candidate vaccine viruses that for the 3C2A, what we
6 call the "Hong Kong/4801-like" viruses, there was a lot of work
7 ongoing in multiple re-assorting labs, including Dr. Boucher's
8 lab in New York, to make candidate vaccine viruses available for
9 the 3C2A subgroup.

10 And so, in September, we had a body of data that was
11 more convincing to us, that the Hong Kong/4801-like viruses were
12 not only genetically a better match for the predominant
13 circulating strain, but that if you looked at the egg-grown
14 viruses, the antisera in our antigenic tests appeared to do a
15 better job of covering the circulating viruses than did the
16 antisera to the egg-propagated Switzerland.

17 And so, it was the decision in September -- and again,
18 now, in February at WHO was really an incremental improvement in
19 the (H3N2) vaccine, to really better match what we know is the
20 predominating (H3N2) virus and to be closer to genetically to
21 the virus as it's going to continue to evolve. And we think
22 that it's going to evolve in this direction of the 3C2A viruses.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

154

1 DR. MOORE: And just to follow up, and this refers
2 back to your 22, which is a cladogram for the HA genes, for the
3 (H3N2)'s. The 3C2A group looks, the Hong Kong group, it looks
4 like a fairly distant genetic splinter off of a main group of
5 the 3C2A. So just based on phylogenetic divergence alone,
6 wouldn't it make more sense to pick a strain that is in the
7 center of that clade?

8 UNIDENTIFIED PERSON: (inaudible)

9 DR. MOORE: Yeah. Your phylogenetic tree of --

10 DR. KATZ: Correct.

11 DR. MOORE: -- the hemagglutinin gene.

12 UNIDENTIFIED PERSON: (inaudible)

13 DR. MOORE: It is --

14 DR. KATZ: Twenty-two.

15 DR. MOORE: -- slide 22 that I have in the corner.

16 DR. KATZ: Right. So the Hong Kong is sort of a bet
17 at the base of that, right.

18 DR. MOORE: Right.

19 DR. KRAFT: But so for any virus to be a reference
20 virus, and to be a potential vaccine virus, it has to be sort of
21 a little bit behind. It has to be older than the emerging, what
22 you're seeing here, is that emerging group in the oranges and

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

155

1 greens and blues, of the most recent viruses, but Hong Kong
2 still represents that group very well, even though it's sort of
3 at the base, and a little bit back.

4 And it may actually mean that it is a better -- I'm
5 trying to see where the consensus -- it's right, actually --

6 DR. KATZ: Can I just point it out?

7 (Pause.)

8 DR. KATZ: Thank you. So there's Hong Kong, and right
9 above it, this says, "2016 (inaudible) 3C2A Consensus." So
10 actually, Hong Kong is quite close to the consensus of all of
11 these emerging 3C2A viruses.

12 DR. LYNFIELD: Dr. Andrews?

13 DR. ANDREWS: I don't know if this matters, but are
14 these different subtypes, the type of flu that you get from it,
15 is it just as bad as any other? Because I am thinking that you
16 know viruses could, in a perfect world, drive what -- you know
17 what the -- I mean eventually drive them away, hopefully, but
18 what kinds of variants there are, and whether if we ease off of
19 one, do we let that you know come up in prevalence, if we guess
20 wrong.

21 And with more and people being in health plans, where
22 they get dinged -- I get dinged \$100 a month if I don't, in the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

156

1 State employee plan in Connecticut, if I don't do a whole list
2 of things, including get a flu shot. I would imagine that more
3 and more people are going to be getting this shot, and that it
4 might be, not just something you're reacting to what's going on,
5 but you might be able to drive it.

6 And are there variants that really make people very,
7 very sick that are more likely to kill, and we want to make sure
8 that's included. That gets a higher priority on the list, even
9 though it may not be as prevalent. Was it a stupid question?

10 DR. KATZ: No, it's not a stupid question. So I would
11 say, I mean it's clear that we have an (H3N2) season, a
12 predominant (H3N2) season. There's a higher morbidity,
13 particularly in the older adult population, and we tend to have
14 what we call more severe seasons.

15 Is one subgroup, you know more responsible or cause
16 more severe disease? We don't think so. We have that question
17 -- moving to (H1N1). We have that question quite frequently,
18 and we've had it again this season, because I think, as I
19 mentioned in my talk, we have had reports, not only in the U.S.

20 There was a report yesterday just from Mexico, from
21 Europe, the Middle East. Whenever we have an (H1N1) pandemic
22 virus season now, it appears to also be associated with more

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

157

1 severe disease in a portion of the population. Again, we don't
2 think there's anything, that there is some unique variance
3 within that are responsible for that severity.

4 We're looking we continue to look at this. We've
5 looked at this for years always taking viruses from severe
6 cases, fatal cases, and looking at their full genome and saying,
7 asking, is there anything different in these viruses, compared
8 with the other viruses of this, from individuals of the same age
9 group, in the same regions, and we really can't see anything
10 unique.

11 I think severity is very complicated, and there are
12 many host-related factors as well. I understand your point. I
13 think we want a vaccine that can be protective against you know,
14 both H1's and ideally, both B's regardless of the level of
15 severity that we might see with one, over the other.

16 DR. LYNFIELD: Thank you.

17 Dr. Bennink?

18 DR. BENNINK: Yeah. I touched on this wrong before,
19 but I want to go back to this, the term "like" in terms of this,
20 and the H3 viruses, and the list of viruses that you know that
21 are here that are possible, in terms of the H3 that are
22 considered "like" in that sense. And if you look at the ones,

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

158

1 at least that the industry sort of listed here, evaluated for
2 this thing. And I don't know if that's the right -- or we could
3 look at the FDA ones.

4 You know, in the data that you presented, the data is
5 not always there for in those tables, at least I didn't -- maybe
6 I just missed it or something, but have you done a really good
7 antigenic comparison of the like viruses that you do, and do you
8 -- the real comfort in terms of saying, you know, any one of
9 these viruses is just as good, whether it's cell-based, whether
10 it's egg, whatever, you're really comfortable that the cross
11 reactions in terms of antigenicity is very good?

12 DR. KATZ: Okay. So I wouldn't look at the list from
13 industry. Some of these are emerging variants and not -- I mean
14 they would be considered Hong Kong/4801-like, but not all of
15 these are representatives of what we would be using as a
16 reference prototype virus, and be considering for vaccine
17 production, at least at this time.

18 So the primary candidate vaccine viruses are Hong
19 Kong/4801 itself; Hong Kong/7127, I believe; New Caledonia/71
20 and I guess I should (inaudible).

21 UNIDENTIFIED PERSON: Yeah.

22 UNIDENTIFIED PERSON: Yeah.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

159

1 DR. KRAFT: The FDA one, yeah. And so, and
2 Victoria/673, although I'm not -- maybe FDA can speak to this --
3 I'm not aware that we have reassortants for that. So these
4 viruses, obviously by their origin, have emerged in different
5 areas. The New Caledonia one was a virus that was developed or
6 isolated by the Australian lab, and was actually one of the
7 earlier proposed vaccine viruses.

8 At that time, we just didn't have enough information
9 about it. We knew it wasn't Switzerland-like, and so, we just
10 didn't have enough information to recommend it as a virus. So
11 it was really only when we identified the group of viruses that
12 what we refer to as "Hong Kong/4801-like."

13 So once we identified Hong Kong/4801 as our sort of
14 prototype virus, what happens is then the different centers go
15 back and look at some of these other candidates, for which they
16 also had an egg-grown virus, and they do antigenic testing, and
17 confirm that the reactivity is sufficiently similar to Hong
18 Kong/4801, that we call it Hong Kong/4801-like.

19 DR. BENNINK: Yeah. I think it would, for me anyway,
20 when we look at them, I think it would be useful, at least as
21 the Committee looks at it, to see, you know, in a sense like you
22 have these table that you have here, an assay where you actually

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

160

1 -- an antigenic assay, where you actually compared those in that
2 sort of sense. Then you know that you're really comparing all
3 of them in that way.

4 DR. LYNFIELD: Go ahead.

5 DR. BENNINK: I'm going to go on a different tangent,
6 and ask Jerry in just a second, because in the previous years,
7 or so, there was some, and it was brought up by the other -- and
8 I'll just make a mention here, if you want to say anything you
9 know in terms of the live attenuated.

10 In the data that the Department of Defense presented
11 here, there was at least one that was statistically saying --
12 that looked like it was, maybe even better than the inactivated
13 in this particular case. But can you give us an update or
14 something, in terms of what kind of interactions, in terms of --
15 that you might have had that you might want to speak about, or
16 not?

17 DR. WEIR: (Inaudible - Off Mic)

18 DR. BENNINK: You would rather not say anything?

19 DR. WEIR: (Inaudible - Off Mic)

20 DR. BENNINK: That's okay.

21 DR. WEIR: (Inaudible - Off Mic)

22 DR. BENNINK: I'm just curious, because we have in the

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

161

1 past, you know had some --

2 DR. WEIR: (Inaudible - Off Mic)

3 MS. GRUBER: I don't think that we can speak here and
4 talk about the specifics, but I guess we can say that we have
5 had discussions with the manufacturer. Yeah.

6 DR. LYNFIELD: Dr. Sawyer?

7 DR. SAWYER: Well, speaking of the different vaccine
8 products available, we could avoid this whole Victoria versus
9 Yamagata debate, if we were using more quadrivalent vaccine.
10 I'm wondering if anybody here knows, for this current season,
11 what the proportion of distributed doses are that are
12 quadrivalent versus trivalent, and if anyone from manufacturing
13 is willing to tell us what the plans might be for the coming
14 year.

15 DR. LYNFIELD: Dr. Katz?

16 DR. KATZ: Yes. I don't have the exact numbers, but I
17 believe it's a little over 50 percent of the influenza vaccine
18 available in the U.S. market is quadrivalent.

19 DR. LYNFIELD: Any comment from the manufacturers?

20 DR. DOWNHAM: It's a long way to walk, to say no, I'm
21 afraid there isn't. I don't have data on the distribution of
22 quadrivalent and trivalents, unfortunately. Sorry about that.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

162

1 DR. LYNFIELD: Other comments or questions?

2 MS. COST: (inaudible) Captain Cooper, I'm allowed to
3 comment for DOD. I can just speak to the fact of what we saw on
4 the active duty population, that about 30 percent of the active
5 duty population received the quadrivalent vaccine. The rest was
6 receiving the trivalent vaccine.

7 DR. LYNFIELD: And I'm sorry. Can you state your --

8 MS. COST: I'm sorry. Angela --

9 DR. LYNFIELD: -- name and your --

10 MS. COST: Angela Cost, with the Armed Forces Health
11 Surveillance Branch.

12 DR. LYNFIELD: Thank you very much. Are there any
13 other points for discussion? Dr. Wharton?

14 DR. WHARTON: Well, I have to say, from having
15 attended this Committee for a number of years, it is gratifying
16 that we now do have quadrivalent vaccines that contain both B
17 lineages, because historically, this was such a difficult
18 decision for the Committee.

19 The information is -- you know, it's very challenging
20 to make that decision. And it really was out of dissatisfaction
21 with our ability to make a prediction that was very accurate
22 that really led to the Committee's interest in the development

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

163

1 of vaccines that include both B strains.

2 And of course it is wonderful that we now have them
3 from multiple manufacturers and that they account for a
4 significant part of the market. But there still seems to be
5 some issues that I have to say, I don't fully understand, around
6 the (H3N2) component. And I wonder if, at some meeting in the
7 future, it might be possible to spend a little time delving into
8 that complex set of issues a little bit more deeply, to see if
9 there's -- to get a better understanding of it, and identify any
10 issues that might be amenable to better solutions.

11 DR. LYNFIELD: And can you articulate a little further
12 what you have in mind? Is it the challenge of vaccine
13 ineffectiveness amongst (H3N2)? Are there other issues?

14 DR. WHARTON: Well, I am probably not the person best
15 suited to answer that, but there appear to be a variety of
16 complex issues related, both to the biology of the virus itself,
17 our ability to -- the laboratory methods we have to evaluate it,
18 and the complexity of those, as well as vaccine effectiveness,
19 and it's probably some other things, too.

20 DR. LYNFIELD: And I'm going to take the Chair's
21 prerogative, and ask Dr. Monto, did you have a comment regarding
22 the (H3N2) situation?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

164

1 DR. MONTO: Yes. I think I agree totally. We've got
2 a problem here, which has been going on for a number of years.
3 Last year, it was even worse because we had drift, in addition
4 to the issues of the H3 not behaving as well as we would like,
5 in terms of vaccine effectiveness. This is the component of the
6 vaccine we most need to work because it's the (H3N2) that causes
7 typically most of the excess mortality we see in the risk
8 populations.

9 There's also an issue, which has emerged again and
10 again in different studies of prior year vaccination. Here,
11 we're recommending that vaccine be used on an annual basis. And
12 is there a way through strain selection that we can avoid this
13 kind of an issue?

14 It seems to be more an (H3N2) issue. I think it may
15 require an interagency kind of response, rather than simply an
16 FDA response. But the FDA can take the lead, given the role of
17 strain selection and other activities that FDA carries out, in
18 organizing some kind of -- maybe an appropriate meeting targeted
19 on this question would be the first step, and then it could be
20 figured out, how to address it, in terms of the different
21 components of the government.

22 DR. LYNFIELD: Dr. Kotloff?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

165

1 DR. KOTLOFF: Something that I'm having a hard time
2 getting kind of my brain around, is the substantial variability
3 in vaccine effectiveness estimates, and it would seem that you
4 know I think it's very nice when you have a, kind of convenient
5 sample of cases and test negative controls, and can measure
6 effectiveness.

7 But I think for many reasons, including you know what
8 we tell the public about the value of this vaccine, and
9 understanding the value of the different formulations of
10 vaccines against different influenza types that if we could
11 really systematically have a well-designed powered vaccine
12 effectiveness trial, on an annual basis.

13 I don't think the sample sizes are huge for this type
14 of study, but that covered both effectiveness of the live and
15 the inactivated vaccine, that looked seriously at different age
16 groups and was powered to look at that. And then of course
17 that's able to look at different strains of flu, which is harder
18 for us to control. But it just seems that's such an important
19 piece of information that's missing.

20 DR. LYNFIELD: So I don't know if Melinda or Jackie
21 want to comment. I know CDC does have a VE Network.

22 DR. KATZ: Yeah. I think we're trying to do that.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

166

1 And you heard some of the interim estimates presented today.
2 It's just at this time of year we're never going to have the
3 final result.

4 But the CDC has, since I think 2004-2005, has
5 initiated the U.S. Vaccine Effectiveness Network and its
6 multiple sites, it's very large numbers of individuals enrolled,
7 and I think it's -- I mean there's always ways to do things
8 better, but we are a little bit at the whim of what's
9 circulating that year, and when it's circulates, to really be
10 able to provide the estimates. But I think they're --

11 UNIDENTIFIED PERSON: That there will be more end of
12 season.

13 DR. KATZ: There will be, yeah. We'll have the final
14 data sort of coming out, and yeah, Arnold is the expert on this.

15 DR. MONTO: Well, we're one of the sites.

16 DR. KATZ: Right, of course.

17 DR. MONTO: And so I can speak to the kind of approach
18 that is used, which is not a convenient sample. There are clear
19 eligibility characteristics for being considered as somebody
20 whose test is either positive or negative; in other words,
21 whether they test positive for flu, or negative for flu. The
22 network has five sites; it's being re-competed right now.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

167

1 There's also now, a vaccine effectiveness hospital
2 network. This is the first year of the hospital network,
3 because one of the deficiencies was that we were looking at
4 ambulatory cases and the hospital, the more severe illnesses
5 were being missed, and very often, the illnesses in older
6 individuals, because ambulatory networks typically don't take
7 care of a whole lot of older people. They take care of a lot of
8 younger people.

9 The problem in these networks is that we are totally
10 dependent on the vaccines that are used. It's observational,
11 therefore, given the issues related to the live attenuated
12 vaccine, we are probably going to see less live attenuated
13 vaccine use in the current year. The data from the network was
14 very useful in past years to evaluate the live attenuated
15 vaccine.

16 Similarly, we are going to find it difficult to draw
17 conclusions about the multiplicity of different kinds of
18 influenza vaccines that are coming out, in terms of varied
19 effectiveness, if such differences exist. So, but there are
20 ways around this in terms of targeting, if you could target
21 certain areas where these networks are existing, in terms of
22 what vaccines are used.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

168

1 But it's been a -- I think it's because of these
2 networks that we are now recognizing that there is a problem
3 with the (H3N2) vaccine. And one thing that is very clear,
4 given the similarity over the years in methodology, we can now
5 create a hierarchy of which vaccines are working reasonably
6 well, and which are not, and the one that isn't is (H3N2).

7 DR. LYNFIELD: I think what I would like to do is just
8 have the opportunity to go person by person around the table,
9 and just make sure there aren't any other questions or issues to
10 bring up.

11 So Karen, let's start with you.

12 DR. KOTLOFF: I've asked my question, thanks.

13 DR. SAWYER: I'm good.

14 DR. MOORE: Just a brief comment or maybe it's a
15 question. And it seems to me, as a non-expert in flu that we're
16 missing a very key component, in predicting vaccine efficacy
17 based on HI testing alone, which is, the vast majority of the
18 immunologic data that we're given by CDC and WHO.

19 And so, one thing that I think might be helpful, is,
20 if we now at this point in time, step back and say, what other
21 immunologic tests, whether it's neuts, whether it's NA testing,
22 or even NA expression, obviously some strains are very low

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

169

1 expressers that are a little bit more predictive, in what
2 vaccines are likely to have broad cross-reactivity, rather than
3 focusing only on HI data alone, or at least primarily on HI
4 data, and then HI genetics. That worries me at least a little
5 bit, as a non-expert in evaluating this.

6 DR. KATZ: So are you worried about the focus on the
7 hemagglutinin, or just the fact that we use the focus on the HI
8 assay, itself because we are, for (H3N2)'s for sure, using
9 neutralization tests more and more. The issue is, if we have to
10 characterize thousands of viruses, antigenically with the
11 reference ferret antisera, the HI is the quickest, fastest, and
12 most efficient way to do that.

13 We're working on developing higher throughput
14 approaches for the neutralization assay. We're just not quite
15 there yet.

16 DR. MOORE: Bravo.

17 (Laughter.)

18 DR. MOORE: Please do that. At least I would think, I
19 would feel much more confident on those data than any variant of
20 HI alone. And I know that it's very hard because you do have to
21 do things rapidly, and it's a relatively easy test, but for some
22 reason, we're just not capturing all the data we need, in order

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

170

1 to make a really good prediction as to what is a broadly
2 efficacious vaccine, it seems to me.

3 DR. LYNFIELD: Yes, Dr. Ye?

4 DR. YE: Well, I just want to comment on the assays.
5 I think, now, for the human serology studies, we also include
6 microneutralization in human serology studies, and that I think
7 is similar to the study using ferret. Other than, in the human
8 we confirm that the assay, you know HA assay.

9 So you know whatever the result come from the HI
10 similar to the assay from microneutralization. And those are, I
11 think for HI assay, you are looking for the virus entry that
12 bind to the host receptor. In the first step of an infection,
13 where, the microneutralization you're looking for the whole
14 cycles of the replication that not only look for HA assay, or HA
15 function, but also looking for some NA function, because unlike
16 HI assay, you can add any inhibitors, just measure HA assay.

17 Where, in microneutralization you cannot add anti-HA
18 there because you abolish virus replication you cannot do it
19 anyway. I think both assay they are an advantage and a
20 disadvantage. You've got to add together to give you whole
21 picture.

22 DR. LYNFIELD: Thank you. Dr. Long?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

171

1 DR. LONG: Infectious disease doctors like single
2 pathogens, a good vaccine that works once, lasts a lifetime, and
3 the disease is gone. So I always come to this meeting,
4 influenza, paying really careful attention. And by ten o'clock
5 I have a very big headache because the pathogen never stays the
6 same.

7 It's very, very clever. There are many, many, many
8 pathogens under the rubric of influenza. It's a mucosal
9 disease. A natural disease doesn't provide long-term
10 protection.

11 We are trying to go about at this by multiple ways;
12 none of them is perfect even for the short time after the
13 vaccine is administered. So I'm comfortable trying to follow
14 the footprints of the virus that we have seen today, I think,
15 pretty elegantly, put out in front of us.

16 And I'm very pleased with what happened in the last
17 year of the predictions, in the match. And so I'm trying to
18 concentrate a little bit more. I'm not trying to solve a big
19 influenza problem today, but trying to with the things that we
20 have in front of us, what's the best direction to go. So I'm
21 good.

22 DR. LYNFIELD: Great. Dr. Monto?

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

172

1 DR. MONTO: Well, I think I've said enough, but I'll
2 add one point, and that is, last year our outbreak in Michigan
3 and in much of the country, was an a H3 [sic] AA32C virus. And
4 Switzerland, which is currently in the vaccine, would not have
5 matched it. So that's for me the reason to move on, to the Hong
6 Kong.

7 DR. MCINNES: I have no questions, no comments.

8 DR. LYNFIELD: Thank you. Okay. Dr. Gruber, yep, but
9 maybe she would like to make a comment.

10 DR. GRUBER: I do not want to make a comment.

11 (Laughter.)

12 DR. LYNFIELD: Okay. Thank you.

13 DR. GOLDBERG: Hi. This is Dr. Goldberg.

14 DR. LYNFIELD: Great.

15 DR. GOLDBERG: Am I correct, in assuming that if we go
16 with these recommendations, there will not really be any kind of
17 production delay?

18 (No response.)

19 DR. GOLDBERG: Of any significance? Or am I, did I
20 miss something?

21 DR. LYNFIELD: One of the manufacturers will come to
22 the microphone.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

173

1 DR. GOLDBERG: Okay.

2 DR. LYNFIELD: And can you be a little more specific,
3 Dr. Goldberg, in what you're asking when you say, "These
4 recommendations"?

5 DR. GOLDBERG: Well, I guess, I mean it's hard because
6 I don't have any hard copy of the presentation, but as I was
7 looking at it, it did not appear from the slides, that with
8 these recommendations for any changes, that there would be
9 anything that resembled a really significant delay in
10 production, because there was too much to do to get it to work.

11 DR. LYNFIELD: Okay. So to clarify, when you say
12 "these recommendations," are you --

13 DR. GOLDBERG: The manufacturer --

14 DR. LYNFIELD: -- referring to --

15 DR. GOLDBERG: -- if we (inaudible) --

16 (Crosstalk)

17 DR. LYNFIELD: -- to the ones --

18 DR. GOLDBERG: -- the changes.

19 DR. LYNFIELD: -- that the WHO recommended, or --

20 DR. GOLDBERG: Right.

21 DR. LYNFIELD: -- what are -- okay.

22 DR. GOLDBERG: Right. Sorry.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

174

1 DR. LYNFIELD: No, no.

2 DR. GOLDBERG: Okay.

3 DR. LYNFIELD: I just want to clarify that. So you're
4 asking if we followed the WHO's recommendations from last week,
5 would one expect an on-time process.

6 DR. GOLDBERG: Relatively on time, yeah.

7 DR. DOWNHAM: I suggest the answer to that is we would
8 be able to meet the timelines per usual. Going back to the
9 meetings that we've had through the WHO, through the course of
10 2015, many within the manufacturing sector have the head's up
11 there was a likely change, particularly with the (H3N2)'s. So
12 obviously I can't speak for all manufacturers, as usual, but I
13 would suspect that we are all bases loaded and ready to go.

14 DR. GOLDBERG: Thank you.

15 DR. LYNFIELD: Thank you.

16 DR. GELLIN: So just on a finer point, Matthew. So,
17 but weren't the strains that are on the table now, are those
18 that have been in the vaccine, in the southern hemisphere for
19 the past six plus months. Right?

20 MR. DOWNHAM: Correct.

21 DR. GELLIN: Okay. Thank you.

22 DR. BENNINK: I think -- I'm fine, thank you.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

175

1 DR. LYNFIELD: Okay.

2 MS. ANDREWS: I don't have any more questions, but
3 just a comment. I'm new to this Committee, and a consumer
4 representative (inaudible) on health systems. I'm really
5 impressed by how much working butt goes into the flu vaccine,
6 and you know the fact that you get it wrong, now I get why.

7 (Laughter.)

8 MS. ANDREWS: My head hurt by ten o'clock, too. I'm
9 impressed.

10 (Laughter.)

11 COL STANEK: This is Colonel Stanek. I don't have any
12 issues, but I do want to say that obviously it's a difficult
13 decision, and every year that I come to this meeting, I always
14 appreciate the in-depth discussion and the presentations that we
15 get, really are unparalleled. So thanks, to everyone who helps
16 give those presentations.

17 DR. KATZ: I just want to apologize for making
18 everybody's heads hurt.

19 DR. WHARTON: I don't have any questions. I would
20 like to say that it's amazing the amount of information that's
21 available, and I think that is part of the reason why it gives
22 people a headache. There's a huge amount of information that is

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

176

1 collated globally.

2 There are choices to be made. There are decisions
3 because there are options, because we have so much information,
4 and that's really a better place to be than having less.

5 DR. AIR: Yes. I also would like to congratulate
6 everyone on the amount of information, and also the realization
7 for Dr. Katz and Dr. Ye that you have to look at the whole virus
8 life cycle to predict the effect, and not just binding. And I
9 think this is a big step forward.

10 DR. GELLIN: I don't have anything else to add, except
11 that as we all learn, while we do this once a year, and the flu
12 season is seasonal, this flu thing is 24/7 365. And Jackie and
13 her team and the vast global team that's responsible for making
14 sure all this happens is doing this every day.

15 DR. LYNFIELD: Dr. Vijh, any comments?

16 DR. VIJH: No.

17 DR. LYNFIELD: No? Yeah. I also really want to
18 express my great appreciation for all the work that people do to
19 be able to bring us these data, and to explain the data to us.
20 So we're very grateful to Jackie, and to the Department of
21 Defense, and to the FDA, and to those associated with the WHO
22 system. So thank you.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

177

1 Okay. Well, I'm going to turn it over to Dr. Vihj for
2 a few moments, who will lead us through the next part of the
3 meeting.

4 **VOTING**

5 DR. VIJH: So basically, we have four questions to
6 vote on, and the Committee has to vote on. They're in front of
7 you on the monitors and the screens. So it's going to be 1(a),
8 (b), and (c), and then 2 for the quadrivalent.

9 So the way it works, if you've not used the system
10 before. In front of your -- on the microphone, you have, it
11 says "yes," "abstain," and "no." So we use an electronic
12 voting system, in which the votes are cast simultaneously.

13 And while you're in the process of voting, the buttons
14 will keep flashing. And Derek there is going to start the
15 machine and it'll start flashing. Whatever you vote, please
16 press yes, no, or abstain, depending on your vote for each
17 question; so 1(a), 1(b), 1(c), and then 2(a), so you'll have
18 four voting things to go through.

19 And while the vote is open, if you'd like to change
20 your vote, simply press a different button, and this will change
21 your vote for the record. While you're voting it's private.
22 And after the buttons are finished flashing and the voting is

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

178

1 officially closed, your vote is locked in, and the vote will
2 then be displayed on the T.V. screen, and I will officially read
3 and tally the votes for the record. Do you have any questions?
4 Anybody?

5 DR. GOLDBERG: Hi, it's Judy Goldberg. How do I vote?

6 DR. VIJH: Yeah, Dr. Goldberg, why don't you, when we
7 go through the process, you can email me your vote, and I can --
8 the machine has been programmed for me to press your vote, and
9 to be displayed on the screen.

10 DR. GOLDBERG: Okay.

11 DR. VIJH: Thank you for asking that.

12 Just give me one second.

13 (Pause.)

14 DR. VIJH: Derek, are we good?

15 (No audible response.)

16 DR. VIJH: So for the first question for the

17 Committee:

18 Question 1(a): "For the composition of the trivalent
19 2016-2017 influenza virus vaccine in the U.S., does the
20 Committee recommend: (a) inclusion of
21 A/California/7/2009(H1N1)pdm09-like virus?"

22 The buttons are flashing on your microphone. Please

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

179

1 press yes, abstain, or no. I'm still waiting for Dr. Goldberg's
2 email.

3 (Pause.)

4 DR. GOLDBERG: I'm sending one, and wasn't fast enough
5 to get them all done.

6 DR. VIJH: So what are you saying? Did you say yes?

7 DR. GOLDBERG: Yes. I sent you the first, it would be
8 question one is answered.

9 DR. VIJH: Okay.

10 DR. GOLDBERG: Do you have it?

11 DR. VIJH: Just a second.

12 UNIDENTIFIED PERSON: Five?

13 DR. VIJH: Yes.

14 DR. GOLDBERG: Okay.

15 UNIDENTIFIED PERSON: Two, one (inaudible).

16 DR. VIJH: So it's the other way around for me.

17 That's okay. Let me just -- give me some, a few seconds to just
18 look at this.

19 Okay. So I'm going to read the vote officially for
20 the record. It's Dr. Bennink, yes; Dr. Andrews, yes; Dr.
21 Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes;
22 Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

180

1 Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and
2 Dr. McInnes also votes yes; so that's a total of 14 unanimous
3 votes of yes for the first question. Thank you.

4 So we can now move on to the second set of strain.

5 Question: "For the composition of the trivalent 2016-
6 2017 --

7 DR. MCINNES: Dr. Vijh? Dr. Vijh, hold on.

8 DR. VIJH: Yes?

9 DR. WEIR: We just noticed -- several people did --
10 the Hong Kong/4804 is actually 4801. So it's a little typo that
11 we'll need to correct for the record.

12 DR. VIJH: So could you please change the 4804 to
13 4801?

14 DR. LYNFIELD: Thank you.

15 DR. VIJH: Derek, are you going to change it?

16 DR. LYNFIELD: Yeah.

17 DR. VIJH: Thank you so much. That's a good catch
18 before we voted.

19 (Laughter.)

20 DR. VIJH: Question 1(b): "For the composition of the
21 trivalent 2016-2017 influenza virus vaccine in the U.S., does
22 the Committee recommend (b) inclusion of A/Hong Kong/4801/2014

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

181

1 (H3N2)-like virus?"

2 So the buttons are flashing in front of you. Please
3 choose one of the options: yes, abstain, or no.

4 So it's Dr. Bennink, yes; Dr. Andrews, yes; Dr.
5 Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes;
6 Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr.
7 Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and
8 finally, Dr. McInnes, yes; so it's a total of 14 votes of yes,
9 unanimous vote. Thank you.

10 Moving on to the next voting question.

11 Question 1(c): "For the composition of the trivalent
12 2016-2017 influenza virus vaccine in the U.S., does the
13 Committee recommend the inclusion of B/Brisbane/60/2008-like
14 virus B/Victoria lineage?"

15 So Dr. Bennink, yes; Dr. Andrews, yes; Dr. Stanek,
16 yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin, yes; Dr.
17 Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr. Sawyer,
18 yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and Dr.
19 McInnes, yes; so again, it's a unanimous vote of 14 yes, for the
20 record. Thank you.

21 Dr. Goldberg, you could send me the vote for the
22 second question. I'm going to read it shortly.

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

182

1 So moving on to the quadrivalent vaccine:

2 Question: "For quadrivalent 2016-2017 influenza
3 vaccines in the U.S., does the Committee recommend the inclusion
4 of a B/Phuket/3703 [sic] 2013-like virus B/Yamagata lineage as a
5 second influenza B strain in the vaccine?"

6 The buttons are flashing on the machine. Could you
7 please vote: yes, abstain, or no.

8

9 DR. KATZ: I think the B/Phuket should be 3073.

10 DR. VIJH: We have to redo this. What is it?

11 UNIDENTIFIED PERSON: 3073.

12 DR. VIJH: Officially?

13 UNIDENTIFIED PERSON: It said 3703.

14 DR. VIJH: Yeah. It's 3073.

15 DR. LYNFIELD: Thank you, Dr. Katz, for noticing.

16 DR. VIJH: So I'm going to read this. Do I need to
17 read it again, though?

18 DR. LYNFIELD: (No audible response.)

19 DR. VIJH: Yeah. Let me read this again for the
20 record.

21 Question 2: "For quadrivalent 2016-2017 influenza
22 vaccines in the U.S., does the Committee recommend the inclusion

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

183

1 of a B/Phuket/3073/2013-like virus B/Yamagata lineage as a
2 second influenza B strain in the vaccine?"

3 Please vote: yes, abstain, or no.

4 So the vote is: Dr. Bennink, yes; Dr. Andrews, yes;
5 Dr. Stanek, yes; Dr. Wharton, yes; Dr. Air, yes; Dr. Gellin,
6 yes; Dr. Goldberg, yes; Dr. Lynfield, yes; Dr. Kotloff, yes; Dr.
7 Sawyer, yes; Dr. Moore, yes; Dr. Long, yes; Dr. Monto, yes; and
8 Dr. McInnes, yes; a vote of 14 unanimous yes.

9 So that concludes the voting for today's meeting. I
10 hand over the meeting to Dr. Lynfield.

11

12 **ADJOURNMENT**

13 DR. LYNFIELD: Well, I want to thank all the members
14 of the Committee, as well as the experts who have informed the
15 Committee, as well as the manufacturers and the public. I think
16 this was a wonderful meeting. I think it is always a great
17 challenge, as has been articulated, and really appreciate
18 everyone's help and expertise in thinking this through. Thank
19 you. And safe travels.

20 DR. VIJH: Thank you Dr. Lynfield for chairing today's
21 session. You did a great job. Thank you.

22 Thank you to all the members.

**Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016**

184

1 (WHEREUPON, at 2:07 p.m., the meeting concluded.)
2

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

185

CERTIFICATE OF NOTARY PUBLIC

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

I, MICHAEL FARKAS, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS
Notary Public in and for the
State of Maryland

My commission expires:
Notary Registration No.:

Capital Reporting Company
DRAFT: Vaccines and Related Biological Products
Advisory Committee Meeting 3/4/2016

186

1 CERTIFICATE OF TRANSCRIPTION

2

3 I, EVE JEMISON, hereby certify that I am not the Court
4 Reporter who reported the following proceeding and that I have
5 typed the transcript of this proceeding using the Court
6 Reporter's notes and recordings. The foregoing/attached
7 transcript is a true, correct, and complete transcription of
8 said proceeding.

9

10

11 3/18/16

12 Date

13 EVE JEMISON, CET-744

14 Transcriptionist