

**FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
171st Vaccines and Related Biological Products Advisory
Committee (VRBPAC) Meeting**

OPEN PUBLIC MEETING

**Web-Conference
Silver Spring, Maryland 20993**

March 3, 2022

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

ATTENDEES

COMMITTEE MEMBERS	
Hana El Sahly, M.D.	Baylor College of Medicine
Paula Annunziato, M.D.	Merck
Adam Berger, Ph.D.	National Institutes of Health
Henry Bernstein, D.O., MHCM, FAAP	Zucker School of Medicine and Cohen Children's Medical Center
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention
Holly Janes, Ph.D.	Fred Hutchinson Cancer Research Center
David Kim, M.D., M.S., M.H.A.	U.S. Department of Health and Human Services
Arnold Monto, M.D.	University of Michigan
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Andrea Shane, M.D., M.P.H., M.Sc.	Emory University School of Medicine & Children's Healthcare of Atlanta
Jay Portnoy, M.D.	Children's Mercy Hospital
TEMPORARY VOTING MEMBERS	
COL Douglas Badzik, M.D, M.P.H.	Office of Secretary of Defense Health Affairs
David Wentworth, Ph.D. (Non-Voting)	Centers for Disease Control and Prevention
SPEAKERS AND GUEST SPEAKERS	
CAPT Lisa Groshkopf, M.D, M.P.H.	Centers for Disease Control and Prevention
Beverly Taylor, Ph.D.	Sequirus
Courtney Gustin, PH, RS, MH.	Armed Forces Health Surveillance Division

FDA PARTICIPANTS/SPEAKERS	
Peter W. Marks, M.D., Ph.D.	Food and Drug Administration
Jerry Weir, Ph.D.	Food and Drug Administration
Celia Witten, Ph.D, M.D	Food and Drug Administration
Robin Levis, Ph.D.	Food and Drug Administration
Doran Fink, M.D, Ph.D.	Food and Drug Administration
Zhiping Ye, M.D, Ph.D.	Food and Drug Administration
Manju Joshi, Ph.D.	Food and Drug Administration
Anissa Cheung, M.Sc.	Food and Drug Administration
FDA ADMINISTRATIVE STAFF	
Prabhakara Atreya, Ph.D.	Food and Drug Administration
Christina Vert, M.S.	Food and Drug Administration
Lisa Wheeler	Food and Drug Administration
Joanne Lipkind, M.S.	Food and Drug Administration
Mr. Michael Kawczynski	Food and Drug Administration

TABLE OF CONTENTS

OPENING REMARKS: CALL TO ORDER, INTRODUCTION OF COMMITTEE	5
ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICTS OF INTEREST STATEMENT.....	6
INTRODUCTION - INFLUENZA VIRUS VACCINE STRAIN SELECTION 2022-2023 NORTHERN HEMISPHERE.....	22
Q AND A SESSION.....	28
U.S. SURVEILLANCE - INFLUENZA ACTIVITY AND VE UPDATE.....	31
Q AND A SESSION.....	47
GLOBAL INFLUENZA VIRUS SURVEILLANCE AND CHARACTERIZATION.....	54
Q AND A SESSION.....	106
DoD INFLUENZA SURVEILLANCE AND MID-SEASON VACCINE EFFECTIVENESS.....	122
Q AND A SESSION.....	140
CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS.....	143
Q AND A SESSION.....	154
COMMENTS FROM MANUFACTURER REPRESENTATIVE.....	155
Q AND A SESSION.....	181
OPEN PUBLIC HEARING.....	186
COMMITTEE DISCUSSION, RECOMMENDATIONS, AND VOTE.....	194

1 to welcome the Committee members, the participants, and
2 the public to the 171st meeting of the Vaccines and
3 Related Biological Products Advisory Committee. I
4 would like to remind all our members to use the raise
5 your hand function whenever you have a question or
6 comment to make, and we will call on your name where it
7 appears. And with that, I want to turn it over to Dr.
8 Atreya. Dr. Prabha Atreya is the Designated Federal
9 Officer for the meeting today.

10 She'll make some administrative announcements,
11 do the roll call, and the conflict of interest. Dr.
12 Atreya?

13

14 **ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION**
15 **OF COMMITTEE, CONFLICTS OF INTEREST STATEMENT**

16

17 **DR. PRABHAKARA ATREYA:** Thank you, Dr. El
18 Sahly. Good morning, everyone. This is Prabha Atreya,
19 and it is my great honor to serve as the Designated
20 Federal Officer, that is DFO, for today's 171st
21 Vaccines and Related Biological Products Advisory

1 Committee meeting.

2 On behalf of the FDA, the Center for Biologics
3 Evaluation and Research, and the vaccines advisory
4 committee, I would like to welcome everyone for today's
5 virtual meeting. Today the Committee will meet in open
6 session to discuss and make recommendations on the
7 selection of strains to be included in the influenza
8 virus vaccines for the 2022/2023 influenza season. The
9 meeting and the topic were announced in the Federal
10 Registered Notice that was published on January 25th,
11 2022.

12 I would like to introduce and acknowledge the
13 excellent contributions of the staff in my division and
14 the great support team we have at FDA in preparing for
15 this meeting. Ms. Christina Vert is my backup co-DFO
16 providing excellent administrative support in all
17 aspects of preparing for this meeting. She will also
18 be participating in conducting the voting process later
19 in the day.

20 Other staff members who contributed are Ms.
21 Joanne Lipkind, Ms. Lisa Wheeler, Ms. Karen Thomas who

1 provided great support in preparing for this meeting.
2 I would also like to express CBER's sincere
3 appreciation to Mr. Mike Kawczynski in facilitating the
4 meeting today. And also, a big shout out to many FDA
5 staff working hard behind the scenes trying to ensure
6 that today's virtual meeting will also be a successful
7 one, like all the previous virtual VRBPAC meetings.

8 Please direct any press or media questions for
9 today's meeting to FDA's Office of Media Affairs at
10 FDAOMA@FDA.hhs.gov. The transcriptionist for today's
11 meeting is Ms. Linda Giles and Ms. Erica Denham.

12 We will begin today's meeting by taking a
13 formal roll call for the Committee members and the
14 temporary members who are participating. When it is
15 your turn, please turn on your video camera, unmute
16 your phone, and then state your first and last name.
17 And when finished, you can turn off your camera so we
18 can proceed to the next person.

19 Please see the member roster slides in which
20 we will begin with the Chair. Mike, next slide,
21 please. Dr. El Sahly, can we start with you, please?

1 **DR. HANA EL SAHLY:** Morning, everyone. Hana
2 El Sahly, professor of molecular virology and
3 microbiology at Baylor College of Medicine. My line of
4 work is adult infectious diseases, and my research
5 focuses on clinical vaccine development.

6 **DR. PRABHAKARA ATREYA:** Thank you. Dr.
7 Annunziato.

8 **DR. PAULA ANNUNZIATO:** Good morning. My name
9 is Paula Annunziato. I lead vaccine clinical
10 development at Merck, and I'm here today as the non-
11 voting industry representative.

12 **DR. PRABHAKARA ATREYA:** Thank you. Dr.
13 Berger.

14 **DR. ADAM BERGER:** Hi, I'm Adam Berger, the
15 director of the division of clinical and healthcare
16 research policy in the Office of Science Policy, which
17 is part of the director's office of NIH.

18 **DR. PRABHAKARA ATREYA:** Thank you. Dr.
19 Bernstein.

20 **DR. HENRY BERNSTEIN:** Good morning. I am Hank
21 Bernstein. I'm a professor of pediatrics at Zucker

1 School of Medicine in New York.

2 **DR. PRABHAKARA ATREYA:** Thank you. Dr.
3 Chatterjee.

4 **DR. ARCHANA CHATTERJEE:** Good morning,
5 everyone. My name is Archana Chatterjee. I am the
6 dean at the Chicago Medical School and vice president
7 for Medical Affairs at Rosalind Franklin University in
8 Chicago. My area of expertise is in pediatric
9 infectious diseases with a concentration in vaccines.
10 Thank you.

11 **DR. PRABHAKARA ATREYA:** Thank you. Next, we
12 have Captain Amanda Cohn.

13 **CAPT. AMANDA COHN:** Good morning, everyone.
14 I'm Dr. Amanda Cohn. I'm a pediatrician at the Centers
15 for Disease Control and Prevention with expertise in
16 vaccines and public health.

17 **DR. PRABHAKARA ATREYA:** Thank you. Next, Dr.
18 Holly Janes. Maybe she will join. Oh, you got it.
19 Okay, great. Go ahead, Holly. We can't hear you.
20 Still can't hear you.

21 **MR. MICHAEL KAWCZYNSKI:** There you go. Go

1 ahead, Holly. I unmuted you.

2 **DR. HOLLY JANES:** Thank you. I'm a professor
3 at the Fred Hutchinson Cancer Research Center. My
4 training is in biostatistics, and I work in vaccine
5 trial design and evaluation. Thank you.

6 **DR. PRABHAKARA ATREYA:** Thank you. Next up,
7 Dr. David Kim.

8 **MR. MICHAEL KAWCZYNSKI:** Dr. Kim's not with
9 us, yet. He's still logging in. So, let's jump onto
10 the next one, please.

11 **DR. PRABHAKARA ATREYA:** Okay, thank you. Dr.
12 Monto.

13 **DR. ARNOLD MONTTO:** I'm Arnold Montto. I am now
14 Professor Emeritus in epidemiology and public health at
15 the University of Michigan, and I work on influenza and
16 coronaviruses, both evaluation of the vaccines and
17 examining vaccine effectiveness.

18 **DR. PRABHAKARA ATREYA:** Thank you. Dr. Jay
19 Portnoy.

20 **DR. PAUL OFFIT:** Oops.

21 **DR. PRABHAKARA ATREYA:** Sorry. Dr. Paul

1 Offit.

2 **DR. PAUL OFFIT:** Yeah, good morning. My
3 name's Paul Offit. I'm a professor of pediatrics at
4 the Children's Hospital Philadelphia and the University
5 of Pennsylvania School of Medicine. My expertise in
6 the area of vaccines.

7 **DR. PRABHAKARA ATREYA:** Thank you, Dr. Offit.
8 Next, Dr. Portnoy.

9 **DR. JAY PORTNOY:** Great. Thank you. We
10 wouldn't want to miss Dr. Offit's introduction. I'm
11 Dr. Jay Portnoy. I'm a professor of pediatrics at the
12 University of Missouri Kansas City School of Medicine.
13 I'm an allergist/immunologist at Children's Mercy
14 Hospital in Kansas City.

15 **DR. PRABHAKARA ATREYA:** Thank you. Next, we
16 will do the roll call of our -- introduce the temporary
17 voting and non-voting members. Colonel Douglas Badzik
18 -- Andrea Shane, I'm sorry. Go ahead, Dr. Shane.

19 **DR. ANDREA SHANE:** Good morning, everyone.
20 I'm Dr. Andrea Shane. I'm a professor of pediatric
21 infectious diseases at Emory University School of

1 Medicine and Children's Healthcare of Atlanta, and my
2 area of expertise is pediatric vaccines and
3 epidemiology. Thank you.

4 **DR. PRABHAKARA ATREYA:** Thank you. Next, we
5 will introduce Dr. Badzik. Can't hear you, Dr. Badzik.

6 **MR. MICHAEL KAWCZYNSKI:** Yep, you got to
7 unmute yourself, sir.

8 **DR. DOUGLAS BADZIK:** All right. Sorry about
9 that, everyone. Dr. Doug Badzik. I am the director of
10 preventative medicine for the Office of the Secretary
11 of Defense for Health Affairs, and I am a preventative
12 medicine physician.

13 **DR. PRABHAKARA ATREYA:** Thank you. Next, our
14 non-voting member David Wentworth.

15 **DR. DAVID WENTWORTH:** Good day, everybody. My
16 name is David Wentworth, and I am with the Centers for
17 Disease Control. I'm the branch chief for the Virology
18 Surveillance and Diagnostics Branch in the Influenza
19 Division. And I'm also our WHO Collaborating Center
20 director. Thank you.

21 **DR. PRABHAKARA ATREYA:** Thank you. Next, I

1 would like to introduce the FDA staff. First, I would
2 like to introduce Dr. Peter Marks, the director of the
3 Center for Biologics and Jerry Weir who is also
4 involved. Dr. Marks, can you address the Committee?

5 **DR. PETER MARKS:** Hey, good morning. Thanks
6 very much. Well, I'll take this opportunity to just
7 welcome everyone and to thank everyone for taking the
8 time today. Despite all of what we've been through
9 with coronavirus in the past two years, we still have
10 to take the threat of influenza very seriously. And so
11 I greatly appreciate your participation today. Thanks
12 very much, and we look forward to a good discussion
13 today. Thank you.

14 **DR. PRABHAKARA ATREYA:** Thank you, Dr. Marks.
15 Now I will proceed with reading of the Conflict of
16 Interest statement for the record. Okay, the Food and
17 Drug Administration, FDA, is convening virtually today,
18 March 3rd, 2022. The 171st meeting of the Vaccines and
19 Related Biological Products Advisory Committee under
20 the authority of the Federal Advisory Committee Act of
21 1972. Dr. Hana El Sahly is serving as the voting chair

1 for today's meeting.

2 The Committee today will meet in open session
3 and make recommendations on the selection of strains to
4 be included in an influenza virus vaccine for the 2022
5 to 2023 Northern Hemisphere influenza season. This
6 topic is determined to be a particular matter involving
7 specific parties. With the exception of the industry
8 representative members, all standing and temporary
9 members of the VRBPAC are appointed as special
10 government employees (SGEs) or regular government
11 employees (RGEs) from other government agencies and are
12 subjected to federal conflict of interest laws and
13 regulations.

14 The following information on the status of the
15 Committee's compliance with the federal Ethics and
16 Conflict of Interest laws, including but not limited
17 to, 18 U.S. Code Section 208 is being provided to
18 participants in today's meeting and to the public.
19 Related to the discussions at the meeting, all members,
20 regular government members, and the special government
21 employees consulted for this Committee have been

1 screened for potential conflicts of interest of their
2 own as well as those imputed to them, including those
3 of their spouse or minor children and, for the purpose
4 of 18 U.S. Code 208, their employer.

5 These interests may include investments,
6 consulting, expert witness testimony, contracts and
7 grants, corporate research and development agreements
8 or CRADAs, teaching, speaking, writing, patents and
9 royalties, and then finally employment. These may
10 include interests such as current or under negotiation.
11 FDA has determined that all members of this advisory
12 committee -- both the regular and temporary members --
13 are in compliance with federal Ethics and Conflicts of
14 Interest laws.

15 Under 18 U.S. Code Section 208, Congress has
16 authorized the FDA to grant waivers to special
17 government employees and regular government employees
18 who have financial conflicts of interest when it is
19 determined that the Agency's need for a special
20 government employee's services outweighs the potential
21 for the conflict of interest created by the interest

1 involved or when the interest of the particular
2 government employee who is not so substantial as to be
3 deemed likely to affect the integrity of the services
4 which the government may expect from the employee.

5 Based on today's agenda, and all financial
6 interests reported by Committee members and
7 consultants, no conflicts of interest waivers have been
8 issued under 18 U.S. Code 208 in connection with this
9 meeting today. We have consultant Dr. Douglas Badzik
10 serving as the DoD representative and a temporary
11 voting member. Colonel Douglas Badzik is a regular
12 government employee serving as a director of
13 preventative medicine in the Office of the Assistant
14 Secretary of Defense Health Affairs and Health
15 Readiness Policy and Oversight in Virginia.

16 He currently serves as the lead preventative
17 medicine policy advisor for the deputy assistant
18 secretary for defense for Health Readiness Policy and
19 Oversight. Douglas Badzik has been screened for
20 conflicts of interest and cleared to participate in
21 today's meeting as a temporary voting member, and he's

1 authorized to participate in Committee discussions.

2 We also have Dr. David Wentworth serving as a
3 temporary non-voting member and speaker for this
4 meeting. Dr. David Wentworth is employed by the
5 Centers for Disease Control and Prevention as the chief
6 of the Virology Surveillance and Diagnostic Branch in
7 the Influenza Virus Division. He's an internationally
8 known expert in influenza virus epidemiology, worldwide
9 influenza disease burden, and influenza virus vaccines.

10 Dr. Wentworth is a regular government employee
11 at CDC and has been screened for conflicts of interest
12 and cleared to participate both as a speaker and as a
13 non-voting member of today's meeting. As a speaker and
14 temporary non-voting member, Dr. David Wentworth is not
15 only allowed to respond to the clarifying questions
16 from the Committee members but also is authorized to
17 participate in Committee discussions in general.
18 However, he's not authorized to participate in the
19 Committee voting process.

20 Dr. Paula Annunziato of Merck will serve as
21 the industry representative for today's meeting.

1 Industry representatives are not appointed as special
2 government employees and serve as non-voting members of
3 the Committee. Industry representatives act on the
4 behalf of all regulated industry and bring general
5 industry perspective to the Committee. They are not
6 screened and do not participate in any closed sessions,
7 if held, and do not have voting privileges.

8 Dr. Jay Portnoy is serving as the consumer
9 representative for this Committee. Consumer
10 representatives are appointed special government
11 employees and are screened and cleared prior to their
12 participation, and they are voting members of the
13 Committee.

14 Disclosures of the conflict of interest for
15 speakers and guest speakers follow all applicable
16 federal laws, regulations, and FDA guidance. The guest
17 speakers for this meeting today are the following. Dr.
18 Lisa Groshkopf, the chief medical officer in the
19 Virology and Prevention Branch at CDC is participating
20 as a guest speaker.

21 Also Dr. Courtney Gustin is a respiratory

1 focus area lead in the Global Emerging Instruction
2 Surveillance Branch in the Department of Defense.
3 These speakers have been screened for conflicts of
4 interest and cleared to participate as speakers for
5 today's meeting.

6 As guest speakers, Dr. Groshkopf and Dr.
7 Gustin are allowed to respond to clarifying questions
8 from the Committee members following their
9 presentation. However, they are not authorized to
10 participate in the Committee discussions or to
11 participate in the Committee voting process.

12 Dr. Beverly Taylor is the head of the
13 Influenza Technical Affairs and Pandemic Readiness
14 within the Technical Operations at Speke. She is
15 serving as a guest speaker from the industry to provide
16 flu vaccine manufacturers' perspective to the
17 Committee. Dr. Taylor is allowed to respond to
18 clarifying questions from the Committee members
19 following her presentation. However, she's not
20 authorized to participate in Committee discussions or
21 in the voting process.

1 FDA encourages all meeting participants --
2 including the open public hearing speakers -- to advise
3 the Committee of any financial relationships that they
4 may have with any affected firms, its products, and if
5 known, its direct competitors.

6 We would like to remind standing and temporary
7 members that, if the discussions involve any of the
8 products or firms that are not already on the agenda
9 for which an FDA participant has a personal and imputed
10 financial interest, the participants need to inform the
11 DFO and exclude themselves from the discussion and the
12 exclusion will be noted for the record. This concludes
13 the reading of the Conflicts of Interest statement for
14 the public record.

15 At this time, I would like to hand over the
16 meeting to our Chair, Dr. El Sahly, to continue the
17 meeting. Thank you all for your attention. Hana, take
18 it away.

19

1 **INTRODUCTION - INFLUENZA VIRUS VACCINE STRAIN SELECTION**
2 **2022-2023 NORTHERN HEMISPHERE**

3
4 **DR. HANA EL SAHLY:** Thank you, Dr. Atreya.
5 Next, I would like to introduce Dr. Jerry Weir. Dr.
6 Jerry Weir is the director of the Division of Viral
7 Products at the Office of Vaccines Research and Review.
8 Dr. Weir will do an introduction on the meeting today.

9 **DR. JERRY WEIR:** Hi. Thank you, and good
10 morning. I'm Jerry Weir, and I'm the director of the
11 Division of Viral Products at CBER. And I'm going to
12 provide a brief introduction, remind everybody why
13 we're here today, and preview the questions that the
14 Committee will vote on. So, we'll go right into it.
15 Shouldn't take very long.

16 So, the purpose of today's VRBPAC discussion
17 is to review influenza surveillance and epidemiology
18 data, genetic and antigenic characteristics of recent
19 virus isolates, virological response to current
20 vaccines, and the availability of candidate vaccine
21 strains and reagents.

1 After that review and discussion, the
2 Committee will make recommendations for the strains of
3 Influenza A, both H1N1 and H3N2; and the B viruses to
4 be included in the 2022/2023 influenza vaccines
5 licensed for use in the United States. As you'll see,
6 we start out, of course, with looking at the
7 recommendations the World Health Organization has made.
8 But it's the responsibility of every national
9 regulatory authority to make recommendations for
10 vaccines in their country, and that is the role of the
11 VRBPAC in this process.

12 So, the type of analysis that you will see
13 today include the epidemiology of circulating strains.
14 This comes from surveillance data from the U.S. and
15 around the world. You'll also hear extensive antigenic
16 relationships among contemporary viruses and candidate
17 vaccine strains. The type of techniques will include
18 hemagglutination inhibition, or HI, microneutralization
19 tests using post-infection ferret sera. You'll also
20 hear about HI and microneutralization tests using
21 panels with sera from humans receiving recent influenza

1 vaccines. They'll also be presentations on antigenic
2 cartography and phylogenetic analysis of HA and NA
3 genes as well as some work on vaccine effectiveness.

4 Okay, to preview where we are, about a year
5 ago -- almost exactly a year ago -- there was a WHO
6 recommendation for the current influenza season, the
7 one we're in now, 2021/2022. The WHO recommendation
8 was made on February 26th. This VRBPAC met about a
9 week later on March 5th. At that time, the
10 recommendation for vaccines in the U.S. included, for
11 Influenza A(H1N1), an A/Victoria/2570/2019 pandemic-
12 like virus for egg-based vaccines; and an
13 A/Wisconsin/588/2019 pandemic-like virus for cell and
14 recombinant vaccines. For the H3N2 component of the
15 vaccines, the recommendation was for an
16 A/Cambodia/e0826360/2020 H3N2-like virus. And all
17 trivalent and quadrivalent vaccines were recommended to
18 have a B/Washington/02/2019-like virus from the
19 B/Victoria strain. The Influenza B component as a
20 second B component for quadrivalent vaccines was
21 recommended to contain a B/Phuket/3073/2013-like virus.

1 Okay, so last week -- I think it was last week
2 -- February 25th, the WHO made a recommendation for the
3 upcoming season, in other words, next winter Northern
4 Hemisphere season 2022/2023. The WHO made the
5 following recommendation. For Influenza A(H1N1), the
6 WHO recommended an A/Victoria/2570/2019 H1N1 virus for
7 egg-based vaccines, and they recommended an
8 A/Wisconsin/588/2019 pandemic09-like virus for cell and
9 recombinant vaccines. For the H3N2 component, the
10 Committee recommended an A/Darwin/9/2021 H3N2-like
11 virus for egg-based vaccines and an A/Darwin/6/2021-
12 like virus for cell and recombinant vaccines. I'm sure
13 you'll fill more in the presentations about what was
14 behind the different recommendations for egg and cell
15 vaccines.

16 The Influenza B component for both
17 quadrivalent and trivalent vaccines, the recommendation
18 was a B/Austria/1359417/2021-like virus from the
19 B/Victoria lineage, and for quadrivalent vaccines
20 containing the above three virus strains, the
21 recommendation for the fourth strain was a

1 B/Phuket/3073/2013-like virus from the Yamagata B virus
2 lineage.

3 So, the Committee today will discuss, as I
4 said, which influenza strain should be recommended for
5 the antigenic composition for the 2022/2023 influenza
6 virus vaccines in the U.S.

7 As always, the Committee will have several
8 options, but the way we do this to try to make it
9 simpler and to streamline it a little bit, the options
10 will be to start with the WHO recommendations, review
11 those, vote on those, and, if the Committee wants to
12 consider something else, they can recommend alternative
13 strains.

14 For example, for the H1N1 components, we can
15 start with -- the Committee can recommend the
16 A/Victoria strain for the egg-based vaccines and the
17 A/Wisconsin strain for cell and recombinant-based
18 vaccines. Or after hearing the data and reviewing the
19 data, the Committee could recommend an alternative H1N1
20 candidate vaccine strains. Similarly, for the H3N2,
21 the Committee can recommend the A/Darwin/9 or the

1 A/Darwin/6 strains recommended by the WHO, or after
2 hearing the data, they can recommend an alternative
3 H3N2 strain.

4 For B, for trivalent and quadrivalent vaccines
5 the Committee can consider a B/Austria strain that the
6 WHO recommended, or they can recommend a different
7 candidate vaccine virus from the same B/Victoria
8 lineage or even recommend a strain from the B/Yamagata
9 lineage. And, finally, for the second B strain to be
10 included, the Committee can recommend a B/Phuket-like
11 virus as recommended or recommend alternative strains
12 for consideration.

13 So, the voting questions, again, to streamline
14 it, we're going to take four votes: one for H1N1, one
15 for H3N2, one for the Influenza B component that is for
16 trivalent and quadrivalent vaccines, and then the
17 fourth vote will be for the second B strain for
18 quadrivalent vaccines. Again, we'll start out with the
19 voting questions. We'll start out with the WHO
20 recommendations, and then we'll go from there. If the
21 Committee recommends that these be the selection, then

1 that will be the vote. If not, then we would
2 reconsider and come up with something else.

3 So, I won't read them all again, they're the
4 same things I just went through with the options. For
5 the Influenza A, we'll consider the A/Victoria and
6 A/Wisconsin strains together. And for the H3N2, we'll
7 consider the two Darwin strains recommended for egg-
8 based vaccines and cell recombinant-based vaccines
9 together. So, I think I'll stop there, and if there
10 are any questions, otherwise we can proceed with the
11 presentation.

12

13

Q AND A SESSION

14

15 **DR. HANA EL SAHLY:** Thank you, Dr. Weir. I
16 would like to invite the Committee to ask questions or
17 provide comments on the presentation by Dr. Weir, and
18 we will begin by Dr. Portnoy. Dr. Portnoy, please
19 unmute yourself and turn your camera to ask your
20 question.

21

DR. JAY PORTNOY: Thank you, Dr. Weir. I

1 guess my question is you've got egg-based vaccines and
2 you've also got cellular recombinant vaccines. When
3 somebody gets a vaccine, do they get only egg or only
4 recombinant or are they mixed together? Or how is that
5 done? And if you get only the egg vaccines, you're not
6 getting the strains from the recombinant vaccines. Why
7 would they be different? Can you explain that, please?

8 **DR. JERRY WEIR:** Okay, so we have lots of
9 licensed vaccine manufacturers. They are either, egg-
10 based vaccines. That's still the majority of the
11 vaccines. We have one cell-based vaccine, and we have
12 one recombinant-based vaccine. So, there is no mixing
13 of egg and cell within a vaccine. Like I said, for a
14 manufacturer that makes an egg-based vaccine, all the
15 strains will be egg-based vaccines. What was the
16 second part of that again?

17 Oh, they get slightly different strains but,
18 yes, all of those strains are supposed to be
19 antigenically similar even though some are better
20 growers and better suited for an egg-based vaccine, or
21 some are better suited for cell-recombinant vaccines.

1 But antigenically they should be the same or very
2 similar.

3 **DR. JAY PORTNOY:** Okay, great. Thank you.

4 **DR. HANA EL SAHLY:** Dr. Weir, I have a
5 question just to tap into your institutional memory
6 here. Did the Committee ever recommend an alternative
7 that was (audio skip)?

8 **DR. JERRY WEIR:** Okay. No, I don't think so.
9 But it can happen, and there have been examples in
10 other countries where that happens. I will say from a
11 practical matter, you might remember that the U.S. has
12 a lot of representation at the WHO meeting. Both the
13 CDC is represented; we at CBER are represented. Saint
14 Jude is represented. So, it's probably unlikely
15 because our views for the U.S. are taken into
16 consideration, but it can happen. And again, influenza
17 viruses tend to circulate and be global, but every once
18 in a while, some area of the world will be a little
19 different from something else. So that is why we have
20 to consider it.

21 **DR. HANA EL SAHLY:** Great. I see no hands

1 influenza surveillance as well as a preliminary interim
2 estimate of vaccine effectiveness for this season.
3 We're going to start with surveillance, and I'm going
4 to be presenting a number of slides from the most
5 recent CDC FluView report and this comes out every
6 week. It will be updated next tomorrow.

7 The most recent report is for Week 7 which is
8 the week ending February 19th, 2022. Before starting,
9 I just want to thank the members listed here of our
10 Influenza Division Domestic Surveillance Team of whom
11 I'd just like to acknowledge for the amazing work they
12 do on a regular basis.

13 So, we're going to start with virologic
14 surveillance today. This first slide summarizes
15 results of influenza-positive test results reported to
16 CDC on a weekly basis from surveillance laboratories
17 located throughout the United States.

18 These laboratories include two basic
19 categories. We have clinical laboratories shown on the
20 left, and public health laboratories shown on the
21 right. We do get slightly different data from each of

1 them. In general, the clinical laboratories might
2 not, for example, perform type and subtype or lineage
3 testing, so we generally end up with fewer colors on
4 that graph. For the clinical labs, they generally do
5 perform type and subtype testing.

6 Looking first at the graph on the left, which
7 is for the clinical laboratories, the bars represent
8 the number of isolates. Yellow represents Influenza A.
9 Green, which is very small in quantity, they represent
10 Influenza B. And the black line represents the percent
11 of respiratory specimens testing positive. The percent
12 of respiratory specimens testing positive peaked
13 initially for the season at Week 50, so approximately
14 mid-December at about six percent and then declined
15 over late December and January to a low of about two
16 percent by Week 2 of the year.

17 Since that time, the percent of specimens
18 testing positive have begun to creep up again, and it's
19 increased over the past couple of weeks by 4.2 percent.
20 The previous week was three percent. Again, as you can
21 see, most of the graph is yellow. We have most

1 positive specimens testing for Influenza A as denoted
2 by the yellow bars.

3 For the public health laboratory figure on the
4 right, this shows that the red color represents H3N2.
5 The majority of the viruses subtyped -- and those are
6 in red -- are H3N2 viruses.

7 Next, we're going to move on to influenza-like
8 illness surveillance. One point to note about the
9 slides that follow that discuss illnesses or
10 hospitalizations or deaths, some of these surveillance
11 systems track laboratory-confirmed influenza outcomes
12 and some of them don't. So, I'm going to try to be
13 careful to point out which do and which don't. This is
14 influenza-like illness activity. This is from ILINet,
15 and this is a network of providers who report weekly to
16 CDC the percent of outpatient visits that were positive
17 for -- that were for the purpose of influenza-like
18 illness or ILI.

19 The system uses a symptom-based or syndromic
20 definition and not laboratory-confirmed flu. So not
21 everything you see here is going to be flu, but it is

1 useful for tracking influenza-like illness activity,
2 which is a proxy for influenza over the course of a
3 season.

4 There are a number of seasons represented in
5 this graph. The current season is represented by the
6 line with the superimposed red triangles. For our
7 current 2021/2022 season, we had ILI activity reported
8 to this system peak in mid to late December. It has
9 since declined below epidemic threshold. There's a
10 slight uptick in the most recent week that's just
11 barely there, and we'll have to see where that goes
12 over the next number of weeks.

13 So, next, there are two slides that summarize
14 hospitalization data from two different reporting
15 systems. This first one is for FluSurv-NET, and this
16 consists of cumulative hospitalization rate data. They
17 are reported on a weekly basis. They are summarized in
18 this slide as cumulative rates. So, we expect that the
19 line is going to go up over the course of time because
20 we suspect that there'll be more hospitalizations over
21 the course of time. It's not presented here as a week-

1 by-week number.

2 Several seasons, again, are represented in
3 this figure. The current 2021/'22 season is
4 represented by the orange line that's rather close to
5 the x-axis. The previous 2020/'21 season is
6 represented by the lower line which hugs the x-axis.
7 As we all know, last season was relatively notable for
8 very low influenza activity. We do have somewhat more
9 during this season.

10 Overall, cumulative hospitalization rates are
11 tracking higher than they were during the 2021 season
12 but are still lower than the previous four seasons that
13 are also represented in this chart. Those are 2016/'17
14 through 2019/'20. Cumulative hospitalization rates
15 thus far for this season is 4.9 per 100,000.

16 This next one also summarizes hospitalization
17 data. This is from a system that's relatively newer to
18 the weekly FluView report. User data from HHS Protect,
19 and they also summarize hospitalizations associated
20 with laboratory-confirmed influenza as did the last
21 slide of FluSurv-NET data. To this system, hospitals

1 report the number of patients admitted with laboratory-
2 confirmed influenza each week. Unlike the FluSurv-NET
3 data on the last slide, this slide depicts
4 hospitalizations by week rather than cumulative rates.
5 So, you don't see a progressive incline upward over the
6 course of time. Similarly, to previous slides, we have
7 calendar week on the x-axis.

8 As of February 2nd, 2022, hospitals are now
9 required to report laboratory-confirmed influenza
10 hospitalizations to this system. Prior to that date,
11 reporting was optional. So, something to keep in mind
12 when you look at the slides. The peak reporting week
13 here was Week 52, the last week of 2021, for which
14 2,616 hospitalizations were reported. This was,
15 however, before reporting became mandatory. So, we can
16 just keep that in mind.

17 For the most current week, Week 7, or the week
18 ending February 19th, 1,420 such hospitalizations
19 reported. You can see a bit of an increase over the
20 last several weeks towards the right-hand side of that
21 graph. And this is something, of course, we'll be

1 continuing to follow. For the total cumulative number
2 of hospitalizations reported to the system was 5,066.
3 But, again, that caveat was that reporting was not yet
4 mandatory for much of this period.

5 Our last surveillance system slide summarizes
6 mortality, and these data come from two different
7 systems which have some different characteristics, so
8 we'll briefly summarize those. The slide on the left
9 shows mortality data from the National Center for
10 Health Statistics Mortality Surveillance System which
11 collects and reports weekly the percent of deaths
12 attributed on death certificates to pneumonia and
13 influenza. So, these are not laboratory-confirmed flu
14 deaths.

15 Since early 2020, this system has also tracked
16 deaths attributed to COVID-19. The red line that
17 snakes across the graph denotes the percent of deaths
18 attributed to all of these causes, while the yellow
19 areas represent pneumonia and influenza specifically,
20 and the blue COVID-19 specifically. For the current
21 reporting week, 22.6 percent of deaths were attributed

1 to pneumonia, influenza, or COVID-19.

2 The right-hand graph summarizes pediatric
3 mortality associated with laboratory-confirmed
4 influenza, which has been reportable in the United
5 States since 2004. And these are deaths that are
6 associated with laboratory-confirmed disease. For the
7 last season 2020/2021, one pediatric death was
8 reported. Thus far, for this season, 2021/'22, a total
9 of six deaths have been reported.

10 So just a brief summary of some points from
11 domestic surveillance as of Week 7. The most recent
12 reporting week, 4.2 percent of specimens submitted to
13 clinical laboratories were positive after having peaked
14 at about six percent initially at Week 50 and declining
15 to two percent. We are seeing an uptick in more recent
16 weeks. We're currently at 4.2 up from 3 percent the
17 previous week, and we will get new reporting data on
18 that tomorrow.

19 Most of the specimens that are subtyped in
20 virologic surveillances are H3N2 viruses. Influenza,
21 overall in the country, activity is sporadic, but it is

1 actually increasing in some parts of the country and is
2 not uniform across the United States but continues to
3 be sporadic and increasing in some parts of the
4 country. The cumulative hospitalization rates, one of
5 our indexes of severe illness -- FluSurv-NET -- is
6 higher for that of the entire 2021 season but lower
7 than that observed at this time during the four seasons
8 preceding the COVID-19 pandemic.

9 So, moving on next are some slides from two
10 sources just to provide some idea of preliminary VE for
11 the season. This first part is just one slide, and the
12 second part's a bit longer. The second part will
13 summarize what we usually cover in this meeting every
14 year, which is a preliminary estimate of VE from the
15 U.S. Flu VE Network. This first slide, there's just
16 one that summarizes some information regarding an
17 outbreak associated with the university campus earlier
18 this year.

19 So, before presenting the Flu VE Network, just
20 to summarize this slide, there is a period of time in
21 October/November during which the overall activity in

1 the United States was low but where influenza outbreaks
2 had been reported on several U.S. university campuses
3 even though the overall activity in the country was on
4 the low side.

5 In this particular outbreak, a large number of
6 influenza positives were detected by multiplex testing
7 in a university campus. Among these, 519, or 20
8 percent, out of 2,882 ill students that were tested at
9 campus health service were Influenza A positive.
10 Direct sequencing of these viruses from clinical
11 specimens identified Influenza A(H3N2) HA subclade
12 3c.2a1b group 2a.2.

13 The overall efficacy in this population over
14 the course of this outbreak was zero. Overall, the
15 rates of vaccination were similar for both groups, the
16 infected and the non-infected. There were more details
17 about this that were published in an MMWR earlier in
18 the fall. So, this provided an early index of VE while
19 overall activity was still low.

20 So, moving onto the Flu VE Network. Last year
21 at this time when we spoke, we were in a period of

1 pretty much historically low influenza activity, and
2 there was not enough information with which to get a VE
3 estimate last season. We are seeing a bit more
4 activity this season as you can see from surveillance
5 and are able to have a preliminary VE estimate. There
6 are some caveats associated which we'll go over at the
7 end, but we'll present what we have thus far.

8 So, this estimate comes from the U.S. Flu VE
9 Network, which is a network of currently seven sites
10 that provides estimates of influenza vaccine
11 effectiveness using an observational test-negative
12 case-control design each season, and the sites are
13 denoted here on this map. Sorry, I'm having a little
14 trouble changing slides here. I hope you can see it; I
15 can't. So, I'm going to back up. I think this is a
16 network issue. Just give me one second. Okay, so we
17 have our map. Good, okay. So --

18 **DR. HANA EL SAHLY:** We now have interim
19 results slides. Is that what you want?

20 **DR. LISA GROSHKOPF:** Perfect. Okay, so now
21 we match. Thank you very much. I appreciate that.

1 So, this network enrolled outpatient aged six months or
2 older who have acute respiratory illness with cough of
3 less than or equal to seven days duration. The data
4 presented on these slides represent enrollment between
5 October 4th and January 27th. So, they're relatively
6 current, about a month back in terms of when they were
7 summarized. The network, again, uses a test-negative
8 case-controlled design in which the odds of vaccination
9 among the influenza RT-PCR positive cases is compared
10 to (inaudible) of the vaccination among influenza RT-
11 PCR negative controls.

12 So, all of these patients present to an
13 outpatient facility with respiratory illness, and
14 they're sorted into cases or controls based on their
15 test status, which is done by RT-PCR. For these
16 preliminary analyses, vaccination status is defined by
17 receipt of at least one dose of any 2021/'22 seasonal
18 flu vaccine according to medical records, immunization
19 registries, and/or self-report. As these data are
20 completed and we get closer to the end of the season
21 and beyond, those statuses are confirmed. But in some

1 cases this year, we don't have confirmed vaccination
2 data.

3 And VE is calculated in one minus the adjusted
4 odds ratio times 100 percent, and models that are used
5 to do this are adjusted for several potential
6 compounding factors including study site, age, and
7 month of illness onset.

8 So, for the periods of time that we have,
9 which is through January 22nd, 2022, a total of 2,758
10 were enrolled as of that point: 2,611 or 95 percent
11 were flu negative, 147 or 5 percent were flu positive.
12 Among all the subtyped viruses, these were A(H3N2).
13 All sequenced viruses belonged to a single genetic
14 group, and that is 3c2a1b subclade 2a.2.

15 With regard to the VE estimate, just to draw
16 attention to a couple of things in this chart, one is
17 that we do not have enough data with which to make
18 estimates for H1N1 or B, so the estimates here are for
19 all Influenza A and for Influenza A(H3N2). There also
20 really is not sufficient data to be able to make any
21 sort of assessment with regard to specific age groups

1 or specific vaccine types. This is early, and we'll be
2 continuing to follow this and doing those things as is
3 possible if there's sufficient data to do that.

4 But overall in this table, you can see the
5 adjusted and unadjusted VE estimates from these data
6 thus far for the season. For Influenza A, ages six
7 months and older -- the full study population -- the
8 adjusted VE estimate is 8 percent with a 95 percent
9 confidence interval with minus 31 to 36 percent. And
10 for A(H3N2), 14 percent with a confidence interval of
11 minus 28 to 43 percent.

12 Now, I mentioned at the top that there's some
13 important limitations here. And one just general one
14 that's always the case with the preliminary estimates
15 is that they are preliminary, and the amount of
16 influenza activity in any given season, even in the
17 absence of the pandemic, is somewhat variable by the
18 time we get to this point in the year. So, these
19 things will continue to be updated as more data become
20 available, and more analysis will be done as more data
21 are available.

1 Finally, an additional comment is that the VE
2 estimates here are limited to mild illness. These are
3 people that present as outpatients. Evaluation of VE
4 against influenza hospitalizations is ongoing through
5 another network, CDC's HAIVEN Network.

6 And, lastly, just a final acknowledgment to
7 not only the staff of the Flu VE Network and their
8 personnel who collaborate with us but also the U.S. Flu
9 VE Network staff at CDC, my colleagues. Thank you very
10 much.

11

12

Q AND A SESSION

13

14 **DR. HANA EL SAHLY:** Thank you, Dr. Groshkopf.
15)It is time for Committee members to ask questions.
16 And I will begin by asking a question regarding the
17 outbreak on the campus. Was it one campus or more than
18 one? I didn't get that.

19 **DR. LISA GROSHKOPF:** The particular data from
20 there is from one campus, and there's a good summary in
21 MMWR that was published, I believe, in late November.

1 **DR. HANA EL SAHLY:** No hospitalizations, the
2 outpatient group?

3 **DR. LISA GROSHKOPF:** Overall, I'm not
4 certain, but I don't know for sure that there weren't
5 any hospitalizations. However, according to the data
6 in the MMWR, overall, these were mild illnesses.

7 **DR. HANA EL SAHLY:** Thank you. Questions from
8 Dr. Offit. Dr. Offit.

9 **DR. PAUL OFFIT:** Yes. First of all, thank
10 you, Lisa, for that talk. Frankly, this is a mucosal
11 virus-like SARS-CoV-2 virus, so you wouldn't expect
12 necessarily that the vaccine would be great at
13 protecting against mild illness. However, you would
14 like it to be very good at protecting against
15 hospitalization and ICU admission. When we present
16 data like this, sometimes this is picked up by the
17 public, and we've gone through this now with SARS-CoV-2
18 and the COVID vaccines as the vaccine doesn't work.

19 And so it would be really important, I think,
20 to get data out there on what is protection against
21 hospitalization and ICU admission, which is the goal of

1 this vaccine. Can you give me an idea of when you
2 would imagine you would have those data?

3 **DR. LISA GROSHSKOPF:** The work with the HAIVEN
4 Network -- that's actually adults only and not
5 children, so, there's that limitation -- is ongoing,
6 and I don't think they have enough data yet to present
7 any kind of estimate. But we will stay on that. I can
8 also check back with them and see if there's anything
9 that they're ready to report yet. But to my knowledge,
10 I don't think they've seen enough to be able to report
11 anything.

12 **DR. PAUL OFFIT:** Thank you.

13 **DR. LISA GROSHSKOPF:** We do have more flu, but
14 it is still low.

15 **DR. HANA EL SAHLY:** To follow-up to this, we
16 did not see an uptick in childhood mortality like we
17 would other seasons as well, right?

18 **DR. LISA GROSHSKOPF:** No. Fortunately. I
19 mean, unfortunately, we do have six reported, but
20 fortunately, it's not more than that I guess. Is that
21 best way to characterize it? We do have an uptick in

1 activity, and we only saw one reported last season.
2 So, any one is obviously horrible, but we're not seeing
3 a big uptick, at least not currently.

4 It's important to keep in mind, though, that
5 the season's not over yet, and we are starting to see
6 in some of the surveillance indices you could see a
7 little bit of an increase, again, for example, in the
8 percentage of specimens that tested positive and some
9 of the hospitalization indices. So, we'll need to keep
10 an eye on that.

11 **DR. HANA EL SAHLY:** I meant it as a gauge of
12 severity that Paul was alluding to.

13 **DR. LISA GROSHKOPF:** Yeah, true.

14 **DR. HANA EL SAHLY:** Dr. Janes.

15 **DR. HOLLY JANES:** Thank you, Lisa. I was
16 interested in hearing you elaborate on your comment
17 about the healthcare-seeking behavior having been
18 influenced by the ongoing pandemic and the implication
19 that might have or the influence that might have on
20 these interim VE estimates. Can you elaborate on what
21 potential effects that might have? Would you expect

1 that to be differential among the flu positive cases
2 versus flu negative, or would it just essentially
3 affect the denominator for these analyses? If you
4 could comment on that. Thank you.

5 **DR. LISA GROSHKOPF:** I don't know if we have
6 enough information to know whether it would be
7 differential or not, but it's possible that people, if
8 they feel that -- it's possible for, I think, that
9 clinicians might not specifically look for flu, and if
10 they're not using multiple viral test, we might not
11 have that information. It's also possible that people
12 might not be going out to test for flu if they're ill,
13 for example, and staying at home. I don't think we
14 really have a full grasp on how pandemic might've
15 affected those things but those are some of the things
16 that have been raised.

17 **DR. HANA EL SAHLY:** Thank you. Dr. Berger.

18 **DR. ADAM BERGER:** Hi. Thanks, Lisa. That was
19 a great presentation and really appreciate all the data
20 and hard work you've done to collect all of this
21 information for us.

1 I'm going to ask a question that you may not
2 actually have the answer to yet because I noted the
3 whole (inaudible) that you detected are all the H3N2 so
4 far. So, I'm wondering about H1N1 from last season and
5 specifically noticed some of the data that was coming
6 out from the WHO work was indicating that the 5a.1
7 subclade was poorly recognized by antisera. So, could
8 you comment on how prevalent that was last season as a
9 potential expectation from where we see this coming
10 season?

11 **DR. LISA GROSHKOPF:** That's a good question.
12 It might be better addressed by Dr. Wentworth, I think.
13 So, I think I might defer that to him.

14 **DR. DAVID WENTWORTH:** Sure, sure. Yeah. H1 -
15 - and I'll cover it in my presentation a bit later --
16 was very low circulation even globally and very low in
17 the United States so far this season. And so that's
18 really where we are with H1. There were parts of
19 central and western Africa where H1 circulated quite a
20 bit, and some parts of Europe, like France, had pretty
21 high levels of H1. And so, there's a mixed bag, and

1 I'll discuss that between the 5a.1 and 5a.2.

2 **DR. ADAM BERGER:** Thank you.

3 **DR. HANA EL SAHLY:** Thank you both. Dr.
4 Chatterjee.

5 **DR. ARCHANA CHATTERJEE:** Yes, thank you, Dr.
6 Groshkopf, for your presentation. My question is
7 about co-infections of any of the influenza viruses
8 with either SARS-CoV-2 or any other respiratory
9 viruses. Do we have any data on that?

10 **DR. LISA GROSHKOPF:** We don't have a specific
11 surveillance system that tracks that. There certainly
12 have been co-infections reported in the literature, but
13 we don't have any surveillance specific for that
14 particular attribute, no.

15 **DR. ARCHANA CHATTERJEE:** Are there any plans
16 to develop that particularly as SARS-CoV-2 is predicted
17 to become endemic in the future. Are there any plans
18 to track that?

19 **DR. LISA GROSHKOPF:** I can't speak to
20 specific plans at this point, but I can try to get some
21 clarity on that and come back.

1 **DR. ARCHANA CHATTERJEE:** Thank you.

2 **DR. HANA EL SAHLY:** I see no additional
3 questions to Dr. Groshskopf. Dr. Groshskopf, thank you
4 for your presentation.

5 **DR. LISA GROSHSKOPF:** Thank you.

6

7 **GLOBAL INFLUENZA VIRUS SURVEILLANCE AND**
8 **CHARACTERIZATION**

9

10 **DR. HANA EL SAHLY:** Next is Dr. David
11 Wentworth, director of the WHO Collaborating Center for
12 Surveillance Epidemiology and Control of Influenza. He
13 is also the chief of Virology Surveillance and
14 Diagnosis Branch at the E-Influenza Division. He will
15 take us through a worldwide tour of global influenza
16 surveillance and characterization. Dr. Wentworth.

17 **DR. DAVID WENTWORTH:** Thanks very much. And
18 just by way for everybody's knowledge, I have this
19 picture up all the time and I never mention it. This
20 is a picture of an influenza particle. In the light --
21 oops, we moved ahead already. The light blue parts

1 were the hemagglutinin which we'll spend a lot of time
2 talking about. And the dark blue, this is the
3 neuraminidase. You'll see that thing with four versus
4 -- there's many more hemagglutinins on the surface of a
5 particle. So, we'll spend a lot of time talking about
6 that. Let's go to the next slide.

7 Oh, I'm in charge, sorry. So, yeah, this is
8 showing here the WHO-VCM recommendations for the
9 Northern Hemisphere and the meeting that took place
10 last week, and this is benefitted by continuous
11 surveillance that's conducted by the Global Influenza
12 Surveillance and Response System which consists of more
13 than 150 laboratories; national influenza centers,
14 which is what NICs stand for; and led in part by WHO
15 Collaborating Centers, such as your CDC Collaborating
16 Center; WHO essential regulatory laboratories, or ERLs,
17 such as the FDA; WHO H5 reference laboratories. So we
18 also cover zoonotic influenza viruses as part of these
19 meeting and make pre-pandemic vaccine choices for those
20 for stockpiling and readiness.

21 So, the meeting was held from February 21 to

1 24. It was a hybrid of an in-person and virtual
2 meeting. It was chaired by Dr. John McCauley. Mike,
3 do you think you can give me that pointer? Thank you
4 very much. So, Dr. McCauley is here. Oops, it
5 disappeared. Oh, there it is. I'm going to need that
6 to work later, Mike. And then had ten advisors --

7 **MR. MICHAEL KAWCZYNSKI:** So, sir, all you have
8 to do is click and drag it anywhere on the screen you
9 want or do with your mouse.

10 **DR. DAVID WENTWORTH:** Yeah. Hmm. It doesn't
11 seem to be doing it. Now it's moving just
12 sporadically.

13 **MR. MICHAEL KAWCZYNSKI:** I moved it for you.
14 I just wanted you to -- we'll turn it off for right
15 now. Okay, go ahead.

16 **DR. DAVID WENTWORTH:** Yeah, yeah. Turn it off
17 because it's not working. So, there's ten advisors and
18 eight advisors have seasonal influenza and two focus on
19 zoonotic, and they do this as part of their capacity as
20 representatives for their WHO CC or ERL. I'm going to
21 move to the next slide here; we'll get moving.

1 I'm going to move pretty quickly through the
2 global activity. We had a nice presentation by Dr.
3 Groshkopf of the U.S. activity. This slide, I think,
4 is nice because it shows you what normal influenza
5 activity looks like in January of 2020 although it
6 sharply fell as SARS coronavirus rose.

7 But then in July 2020, when we see in the
8 Southern Hemisphere some activity, we didn't see any.
9 Then in January 2021, we had very low activity in the
10 Northern Hemisphere. And then in July of 2021, we also
11 had very low influenza activity. And we started to see
12 a more normal course of activity at the end of 2021 and
13 the beginning of 2022 as you can see here. And most of
14 this was H3N2 globally but with some H1N1 and very
15 little B/Victoria lineage activity, which you can see
16 there. Move to the next -- sorry.

17 This is looking now at the same thing but over
18 many, many years, and it's just to give you an
19 appreciation for what it normally looks like. And then
20 we had that basically big sieve during the COVID
21 pandemic initiation, the first parts of the COVID

1 pandemic where we had very little flu activity.

2 This slide illustrates the percentage of
3 influenza viruses by subtypes and lineage, and so what
4 you can see is that the A viruses dominated for the
5 most part. They represent three-quarters; they're the
6 light blue and the dark blue colors. And the B-viruses
7 are in the orange.

8 And the numbers aren't really that critical.
9 But the B viruses -- really all of them -- were
10 B/Victoria lineage, and with the A viruses, again, the
11 vast majority were H3N2 with a minority of H1N1. That
12 big section of the pie is unsubtyped, but the
13 proportions would be about the same as what is
14 subtyped.

15 This slide shows the influenza activity
16 globally, and so as I mentioned earlier, we still had a
17 relatively mild influenza activity all over the globe.
18 Some of the exceptions are parts of Africa, like I
19 mentioned western Africa, where we saw more H1s for
20 example. And then more towards the south and east, we
21 saw more H3 and B viruses. And then China had really

1 predominantly only Influenza B.

2 This slide just illustrates the countries and
3 locations/regions where viruses were shared with the
4 WHO Collaborating Centers in this reporting period, so
5 you're getting a sense of where the viruses are coming
6 from for analysis.

7 And now I'm turning your attention to the H1N1
8 pdm09 viruses. This is showing the number of pdm09
9 viruses detected by GISRS over a four-year window from
10 2019 to 2022. And so, if you look at more normal
11 distribution, such as in 2019, you saw this big peak
12 early in the year, Weeks 2 through 8 about. And then
13 it tails off and then increases again as the following
14 winter begins around Week 2 and 3.

15 In the more recent times, you can see 2021 and
16 2022 just really very flatline across that entire
17 spectrum, so very low levels of circulation globally.
18 And this is not due to lack of testing. There's a lot
19 of testing going on for influenza viruses. While it
20 fell off very early in the pandemic, it's continued and
21 done a good job in the number of tests that are

1 performed.

2 Now, this shows the influenza activity
3 globally and where we saw some more activity and, as I
4 mentioned, some parts of western Africa. This included
5 some of the coasts like Togo and Ghana, as well as
6 Mauritania you can see had a very high level of
7 activity, and parts of South Africa as well, for
8 example, the country South Africa. We move to the next
9 slide here.

10 Now I'm going to get into some detail about
11 the H1N1 phylogeny and the phylogeography. And so, by
12 that, I mean, where are these specific clades of HAs
13 circulating? And so, I think many of you now -- I show
14 this very high-level, 50,000-foot level view of the HA
15 gene, the tree, kind of in the middle here between the
16 world and the bars with the tick marks in it. And so
17 that's showing you color-coding by region. North
18 America blue, for example. And so, you can see now, if
19 you go up to where it says 2020 and those first couple
20 of columns, those first months of the year -- those
21 represent months of the year -- you can see all the

1 dashes and the coloring of those dashes indicate where
2 those viruses were found, and they're associated
3 directly across with certain clades and subclades
4 within that phylogeny, that phylogenetic tree.

5 And so, this is showing over the course of
6 many years what happened. And you can also see that in
7 the spring of 2020 -- once you get past those first
8 couple of columns -- influenza viruses weren't detected
9 anymore for characterization, and they really didn't
10 pick up again until you started to get into 2021, and
11 the first places you see them is in Africa. So that's
12 towards the bottom of the tree, and they're in the
13 orange. And they represent that 5a.1 group, which the
14 whole group is shown by that big black bar on the far
15 right-hand side, and you can match that up with that
16 portion of the tree. All those viruses are 5a.1
17 viruses. And that's like the Hawaii/70, which was the
18 vaccine virus.

19 And so, you can see that some of those made it
20 through the COVID bottleneck and continue to circulate
21 up until the time of this meeting. So we saw more

1 virus circulation and spreading from Africa now into
2 Europe. So, you can see those green dashes showing up.

3 Now, if we look towards the top of that tree,
4 you can see this very long branch lines with a batch of
5 small little leaves in that branch. They are 5a.2
6 viruses. So, these are new derivative 5a.2 viruses
7 related to that Wisconsin/588 vaccine that Dr. Weir
8 mentioned. And you can see all the red there, and
9 these are primarily circulating actually in India with
10 that red meaning Asia or southeast Asia or south Asia.
11 And then a few of them being detected most recently in
12 Europe as well with the green dashes.

13 And so, what we really saw come through the
14 COVID bottleneck is the bullets indicator: 5a.1 viruses
15 primarily in west Africa and Europe and 5a.2 HA virus
16 from Asia, the Mid-East, and Europe.

17 Now we're going to get a little closer. I
18 think I'm going to try that pointer again, Mike. See
19 if it works. Um, for some reason it's not following.

20 **MR. MICHAEL KAWCZYNSKI:** Click on the pointer,
21 sir, and then just click on the pointer and just drag

1 it around.

2 **DR. DAVID WENTWORTH:** Yep, it's not wanting to
3 do it. Why don't we go ahead -- can you go to the full
4 screen?

5 **MR. MICHAEL KAWCZYNSKI:** You know what, sir, I
6 apologize. I apologize, sir. Hold on one second. All
7 right, we'll turn it off right now, and I'm going to go
8 full screen, okay? Whenever you want, all right, sir.

9 **DR. DAVID WENTWORTH:** Yes, please. I'll just
10 use verbal descriptions and hopefully people will be
11 able to follow. So now this is a close-up view of a
12 phylogenetic tree of more recent viruses, and so here
13 we're looking at the phylogeography of the most more
14 recent period as you can see really just in 2021 and
15 from September through January so this kind of
16 reporting period. And, again, what we can see is that
17 there's big divisions that are demarcated in the
18 phylogenetic tree, if we go from the bottom now to the
19 top of the tree.

20 So unfortunately, it's a very different than
21 the 50,000-foot view which went from the top to the

1 bottom. But as you go from the bottom of the tree, you
2 can see where I've marked that D187. That's the branch
3 point where the 5a.1s formed this group that are like
4 the Hawaii/70 virus, and I've made an arrow there
5 showing you where that Northern Hemisphere 2020/2021
6 cell prototype A/Hawaii/70/2019 was. And that shows --
7 that's a representative of the very first 5a.1 viruses.
8 They often share this D187A. If you really look at the
9 small print that's in black, also a Q189E.

10 Those have continued to circulate and
11 diversify, and as I mentioned primarily in western
12 Africa which you can see the tips that are orange and
13 in Europe which is the tips are green. And so more
14 recently, you see those green tips in say, for example,
15 starting in November and moving into October and
16 January.

17 Then if you go up the tree a little bit,
18 you'll see where I -- and, oh, I should've mentioned
19 back down in the 5a.1s, you see where I wrote that
20 P137F? That's a new subgroup that's evolved. They
21 have this 137 change and the 155E change. Oh, my

1 pointers -- oh, the pointers there. Thank you. It
2 must be Mike directing the pointer. And then where the
3 split for the 5a.2s, which is demarcated by that red
4 bar -- those are all 5a.2 viruses there -- is where
5 that 156K is labeled. And there's a number of
6 substitutions in addition to that that make up that
7 group. And we've had further evolution of those in a
8 virus. So that reference virus of that
9 Wisconsin/588/2019, which is the Northern Hemisphere
10 2021/2022 cell prototype and the recommendation for the
11 '22/'23 season.

12 There has been further evolution where I've
13 marked that 186T, that big branch point there. And
14 that's where you can see this India/Pune virus from
15 NIV. It's got a very long number I'm not going to read
16 to you from 2021. And that's going to be included in
17 some of these serology studies. So, these dark-labeled
18 viruses are included in our serology studies with post-
19 vaccination sera to see how well those new viruses are
20 inhibited by the post-vaccination sera.

21 I think these bullets basically say what I

1 told you and I, in part, put them in there so that
2 those with visual impairments. So, it makes your slide
3 a little smaller, but they understand what the key
4 points are.

5 Now this shows you antigenic cartography, and
6 it's just taking that HI data from tables. There are
7 many, many tables, and I no longer show them to these
8 kinds of audiences because it's difficult to look at
9 all those numbers. But it puts them in a cartographic
10 map where you can see how related the two virus sets
11 are with each other. And so, the viruses from the HA
12 group are all in the 6B.1A subclades 5a.1, which had
13 that 187, and 5a.2 which had the 156K.

14 And I did neglect to point out that we've seen
15 a few 5a.1 viruses -- well, I did point them out --
16 they were the ones with the 137 change, and they also
17 had this G155E which is in a very important position.
18 So, you'll notice 156 has changed in one group of virus
19 and 155 in another. So, this is an important epitope
20 that are targeted by our antibodies and antibodies of
21 animal models.

1 And the clear thing that I want to have you
2 see from here is the clear antigenic distinction
3 between these two groups. Where it says -- you can see
4 the red dot about in the middle of this cartography --
5 that says HI/70/19. That stands for Hawaii/70 cell-
6 based antigen. And the egg-based version of that
7 vaccine is the green egg-shaped antigen. And so, you
8 can see how closely related they are antigenically.
9 And they are covering all those blue dots, which are
10 the most recent viruses that have the 156N. And you
11 can see that the yellow dots are a little bit away
12 forming their own little cluster, and those are the
13 ones with the 155 and 137 substitutions.

14 Now, if you move up towards the top of this
15 map, you'll see the 5a.2 viruses and how the
16 Wisconsin/588 cell antigen really sits right over the
17 top of all the circulating viruses that have been
18 detected recently. So, these include viruses like the
19 ones that I pointed out from India. And then the
20 Victoria/2570 egg vaccine virus showing you there where
21 that antigen sits in relation.

1 And so, one square in this map is
2 approximately a two-fold difference in the HI titer,
3 and two-fold is the error of the assay. So, two-fold
4 is very little, if at anything. And it's when you get
5 to about eight-fold difference that you can be
6 confident that things are antigenically distinct.
7 Okay, that was a long-winded thing, but we're going to
8 see cartography again, and I won't explain it so
9 heavily.

10 So, the take-homes from this are we have two
11 antigenic groups: the 5a.1 which are the 187-like
12 viruses and the 5a.2. We have seen some evolution with
13 the 5a.1 that are forming a little bit of an
14 antigenically distinct cluster, but they are still
15 related to the old 5a.1 viruses. The grey dots, I
16 should've mentioned, represent older virus that have
17 been circulated in the past. And you can see how many
18 H1N1s we've had previously. And so, we just had very
19 few circ viruses for analysis because there's very few
20 circulating right now.

21 Now, this is what is really quite important

1 now, especially when we start thinking about the
2 vaccine, is the post-vaccination sera analysis of H1N1
3 pdm09 viruses. And so, I think we'll just keep it on
4 the bigger line because these are very small print.
5 But what we have is we have representative viruses from
6 the 5a.2 group; those are boxed in blue. And they're
7 going to be going down in the column. So we have the
8 Wisconsin/588 vaccine virus or the Victoria/2570
9 vaccine virus for the cell and egg-based respectively.
10 And then we have this example of the India/Pune NIV
11 323546 virus which has these additional substitutions
12 like the 186T, but it also has 189V and 224E.

13 And what you can see is that we have panels of
14 sera from pediatric populations that range from 6 to 35
15 months and 3 to 8 years, and then 9 to 17 in rows. And
16 then we have adult populations making up many rows from
17 both the U.S., Japan, and the U.K. And then we have
18 older adults from the U.S. and elderly who are greater
19 than 65. These people are not elderly because I'm
20 really approaching that. So, we've got to change that.
21 So, they're 65 or older.

1 And so now what you can do is go back up to
2 the pediatric. These are the most easy, they're naïve,
3 and they're vaccinated just with this 5a.2 vaccine from
4 the Northern Hemisphere. What you can see is they
5 mount a pretty good response to the 5a.2 -- so blue is
6 good -- and when you start getting into the orange,
7 that's when there is a significant difference between
8 the vaccine response, the geometric mean titer against
9 the vaccine, and the geometric mean titer against the
10 antigen. And so then when you look at the 5a.1
11 viruses, you can see that in that pediatric population,
12 that's where it's statistically clear that there's not
13 good reactivity with that group.

14 However, what you can appreciate as you move
15 down into the older people. Those that are vaccinated
16 with either Flucelvax in the top row in the pediatric
17 three to eight or IIV4, which is an egg-based vaccine,
18 we do see some reductions in the geometric mean titers;
19 so, they are coming up as orange. So, you can also see
20 the numbers in the middle there. Those numbers are
21 what the geometric mean titer is, and so if we go to,

1 for example, the IIV4, the geometric mean titer against
2 Wisconsin/588 is 331, and that against Hawaii/70 is
3 171. So, it is reduced in the geometric mean titer,
4 but that's still a pretty good titer. And I'll show
5 you a little more data about that as we go forward
6 here.

7 So what you can clearly see is that there is
8 some reduction to this new India virus, but they're not
9 extremely significant. They're in the light orange,
10 which means the 90 percent confidence interval is just
11 touching the 50 percent bound. That's what that light
12 orange means. And then if you go to the right under
13 the 5a.1 viruses, the one with the 155 substitution has
14 more reductions than the others where you're seeing a
15 better, what we would call, back boost where you see
16 that in blue even though that that wasn't in the
17 vaccine virus. And that you can appreciate, for
18 example, as you get into the adults, it's very obvious.

19 All right, so this slide, again, illustrates
20 what I just told you. The main high points, again, to
21 help visually impaired. I'm going to move to the next

1 one.

2 This slide I think really starts to address
3 the comment by Dr. Offit and discussing VE, and this is
4 a direct measure of individual responses now. So
5 instead of showing you the statistical responses --
6 which is a very high bar. So, we set that bar up 50
7 percent, touching the 50 percent line on purpose
8 because we want to know if the vaccine could be
9 inferior for those viruses. So, it's a non-inferiority
10 statistical analysis. So, we want to know if that
11 could be inferior for viruses as to whether or not it
12 should be changed.

13 The point I'm making on this slide is what
14 really happens when we immunize folks and what happens
15 with their titer. And so, again, we can start with the
16 6- to 35-month-old at the top rows here. The little
17 blue circles represent what the titers were prior to
18 vaccination. So, the geometric mean titer prior to
19 vaccination was seven, and about five percent of those
20 people would've had a titer above or equal to 40, which
21 is a correlate of protection.

1 And then post-vaccination, you can see that
2 the geometric mean titer of this very young age group
3 is 43. We don't get huge responses in pediatric
4 populations. But it moves to 60 percent of those now
5 having titers greater than 40 against that
6 Wisconsin/588. It is an egg-based vaccine in that age
7 group, and so you can see it's even higher against the
8 homologous Victoria/2570 egg antigen. And you get
9 about 60 percent of them that would respond pretty
10 favorably to that new variant, the India/Pune virus
11 with a geometric mean titer of 37.

12 In contrast, the 5a.1 virus of these children
13 look just like the ferrets, where there's a very large
14 difference that they don't get much cross-reactive
15 boost against those 5a.1 viruses in this very young
16 pediatric population. Now that changes when you move
17 to the older pediatric populations such as the 3 to 8
18 or 9 to 17. Let's focus on the Flucelvax in the 9 to
19 17 group that's about the second batch up from the
20 bottom. You can see prior to vaccination with the 5a.2
21 virus that they had a geometric mean titer of 28, and

1 only about 50 percent of them had a titer greater than
2 40.

3 And at post-vaccination, they had a geometric
4 mean titer of 502 -- quite a great boost. And a
5 hundred percent of them now had a titer greater than
6 40, which is a correlate of protection. So not only
7 that -- so that's the homologous virus -- but if you go
8 over to the column with the India/Pune virus, there was
9 a 437 geometric mean titer, and 95 percent of them have
10 a titer greater than 40. And even more important, if
11 you go to the 5a.1 viruses, which circulated
12 previously, you can see that they get a good back boost
13 to Hawaii/70 with a geometric mean titer that's even
14 higher than the prime they received from the
15 Wisconsin/588. And that's why we call it a back boost.

16 And so that would help neutralize any viruses
17 that are circulating in the basic 5.1a [sic] group.
18 And then if we look at the 155 column, you also see
19 what we call a forward boost into protecting against
20 those. So, these are the newer viruses that are
21 circulating where you get a boost to that newer virus

1 with this 588 5a.2 vaccine. And so, it's very out of
2 the genetic group. It has very different
3 characteristics in general, but there's so much
4 conservation that you get a forward boost. And the
5 same thing happens with Togo/881.

6 Okay, so because this is a public meeting, I
7 am trying to present -- we often present the data that
8 says why the vaccine is bad, what the VE is, what these
9 things are. But really, what this is showing is
10 there's very little downside to being vaccinated. And
11 the other big point is in the very young pediatric
12 population if, in the fall, we have a lot of 5a.1
13 viruses, we will be messaging to clinicians that they
14 need to be watching out for flu positivity and treating
15 with antivirals because we can anticipate that a
16 vaccine with a 5a.2 will not protect well against those
17 5a.1 viruses. But that's the only group that that's
18 true in. All these other groups, we have a strong
19 forward boost and back boost.

20 And so, I won't belabor this, but this is the
21 next slide showing you that the adults, they're in

1 better shape because, as adults, we've seen many H1N1
2 viruses in our lifetimes. And you can see, again, that
3 there's -- going to the very first column here -- how
4 good of a forward and back boost we get across these
5 new viruses.

6 So, to summarize the H1N1 story, we saw
7 viruses that were detected in Africa and Europe and the
8 Middle East, Southern Asia, Oceania, and sporadically in
9 a few other regions. The vast majority of the HA gene
10 sequences belong to the 6B1.A5a subclades. I'm sorry
11 for the alphabet soup. But I'm always going to break
12 it down to the most recent subclades of importance such
13 as the 5a.1, which has this D187A I showed you on the
14 phylogenetic tree. And then we've seen very few
15 viruses that are showing some antigenic evolution that
16 has substitutions at the 137 and 155 that we have our
17 eye on.

18 And then the 5a.2 viruses, which are the base
19 have that 156K and these other substitutions that I've
20 listed there, they were predominant in the Middle East,
21 southern Asia, and Oceania. And many of the recent

1 viruses have this 186T along with all those other
2 changes and were represented by that India/Pune virus.

3 And then the ferret antisera clearly show that
4 the HA clades 5a.1 are distinct from HA clade 5a.2
5 viruses. So, it's a real dichotomy, and we see both of
6 them co-circulating. It's just not unusual in flu to
7 see two evolutionary tracks happening simultaneously.
8 And these are really trying to evade the host immune
9 system at different parts of the molecule. So, it
10 makes picking a vaccine more challenging.

11 What helps in picking that vaccine is this
12 post vaccination of sera that was collected from
13 humans. And we have the advantage of this particular
14 selection, which we didn't have in the last selection,
15 was that now we have people that were vaccinated with
16 5a.2 antigens. And what that clearly shows is that the
17 geometric mean titers against viruses representing the
18 5a.2s are recognized well for the most part as were of
19 those of the 5a.1, so, the vaccine-induced antibodies
20 that cross-reacted 5a.1. And this is likely because of
21 D-cell memory responses since 5a.1s have circulated

1 previously and were a component of the 2020/'21
2 vaccine. The exception were the 6- to 35-month-old
3 serum panels. I showed you that in two ways, both with
4 statistical analysis and just direct representation of
5 the data. And these only react with the 5a.2 viruses,
6 and they are very similar to the data that you get from
7 naïve ferrets.

8 So, none of the viruses -- I didn't show you
9 the data, but this is always done so that people are
10 aware. We do look for the evidence of reduced
11 inhibition by drugs against influenza, both
12 neuraminidase inhibitors and the endonuclease
13 inhibitors. And so, the neuraminidase inhibitors, none
14 of them showed reduced susceptibility, and the same was
15 true for the endonuclease inhibitors. That's the
16 polymerase inhibitor. So, one inhibits that
17 neuraminidase molecule, and the other inhibits the
18 viral RNA-dependent RNA polymerase.

19 So, to move on to the H3N2 viruses, these were
20 always the most complex, evolving viruses, the fastest
21 evolving viruses. And typically, you have the lowest

1 VE and there's a variety of reasons for that and we can
2 discuss those maybe at the end. But the number of H3N2
3 viruses detected by GISRS is shown on this slide.

4 I'm just going to focus you on 2021, which is
5 the yellow bar going from Weeks 1 all the way to Weeks
6 52. And you can see how it increased almost in the
7 normal pattern this time around. Beginning around Week
8 43, you can start to see that increase. And you can
9 start to see it fall with the red line coming into Week
10 4 where the data from this particular analysis ends.

11 This slide illustrates where in the world the
12 activity was happening, and you can see a lot of
13 activity in various parts of the world. The U.S.
14 didn't have a huge season. We had a very small season
15 for the most part, not a strong amount of influenza
16 ranging generally from a zero to five percent level.
17 But in other parts of the world, again, in Europe and
18 parts of Africa as well as Russia had a pretty intense
19 flu season and other parts of Asia.

20 I also just want to point out here that you
21 can see in South America, for example, Brazil has an

1 out-of-season flu season. And so, they actually had a
2 flu season that began either very late in their season
3 or very early in their next season. I don't know how
4 you want to describe it, but it's an interseasonal
5 epidemic. But it's caused by these 2a.2 viruses, which
6 I'll point out here.

7 So now, again, we're looking at that black
8 phylogenetic tree kind of in the dead center of this
9 slide and then the color-coding showing you where the
10 tick marks are. And we can look at this, the evolution
11 of the virus since 2020 through 2021 and the beginning
12 of 2022, basically. And you can see that in the
13 beginning, the viruses were either 3a viruses, and they
14 were found in Europe. It was in the early parts of
15 2020, and those green tick marks as you come down that
16 tree. And then we have the 2a viruses, and they split
17 into the 2alb.1, 2alb.2 groups. And then, now you can
18 also see what's come through the COVID bottleneck. And
19 you can see it in Africa. We had 2alb.1a viruses and
20 2alb.1b viruses that still continue to circulate and
21 some of those spreading to Europe and a few other

1 regions.

2 Then, if you come down towards that major part
3 at the bottom of the tree, it includes the 2alb.2,
4 which is that long black bar. That breaks up into the
5 2alb.2b viruses and the 2alb.2a viruses. And so, the
6 2a viruses are the more recent viruses. And the first
7 ones to come through the bottleneck were 2a.1 viruses,
8 and then the second group were the 2a.2 viruses. So,
9 the .2a2 and the .2a1.

10 And so, you can see how those 2a.1 viruses
11 were primarily in Asia and then started spreading to
12 the Middle East and Europe. And that was -- that's
13 what's showing you here in the bullets. And then the
14 2a.2 viruses were in Europe, Russia, North and South
15 America, and it increased from 2021 to 2022. I'm going
16 to move you to the next slide.

17 This is just showing you a more simple blow-up
18 of all those clades, and that's what's called a time
19 tree. So, time is at the bottom rather than genetic
20 distance, which is usually what's the x-axis. And what
21 you can see here, what you can easily appreciate, is

1 about the top half of that tree where you see -- we'll
2 just start at the very top with the dark blueish purple
3 dots. Those are 2a.2 viruses that also have additional
4 substitutions, one including this 53G which it's marked
5 at.

6 And that X represents the vaccine virus
7 Darwin/6, and so that shows you where it sits in the
8 viral evolution. We've also seen the next batch down,
9 the 2a.2s with 53N, they are the light green dots. And
10 2a.2s that are just more of the standard original
11 2a.2s; you can see they circulated earlier in 2021 and
12 really gave rise to these other viruses. And they're
13 in the goldish-yellow colors. So, then you can see the
14 next X and that's the Cambodia vaccine virus, and those
15 viruses that are the blue dots that are the 2a1. So
16 3C.2a1b.2a1 viruses that are circulating.

17 And what you can also appreciate about this
18 graph is that a small proportion of 1a viruses -- which
19 are near the bottom there, they're the yellow dots --
20 and the 1b -- which are the darker green clades -- are
21 still circulating. And so, these are closer related to

1 the older vaccine virus but have made additional
2 substitutions. So, the main point I want you to take
3 away from this is that the 2a.2 viruses now
4 predominate.

5 There's a large cluster of viruses and they
6 continue to diversify. I would also like you to know,
7 you can see where that X is? That shows the month of
8 the year where that virus is isolated, and you can see
9 that this virus, Darwin/6, which represents the 2a.2
10 viruses was isolated about a month after the vaccine
11 consultation meeting and a few, two or three, weeks
12 after we met for the VRBPAC. Just to give you a sense
13 of how fast flu evolves.

14 This slide shows the geographic distribution
15 of all these clades. I don't think we have to get too
16 involved here. I'm probably speaking a little slow.
17 The HA clade 2a.2 predominant globally. The
18 predominance of the subclades differ regionally, and I
19 tried to point that out on a few other slides; but here
20 I can point it out easier, I think. If you look at the
21 D53G viruses with the 156S and 157I, those are the

1 purple kind of color, you can see they really
2 predominate in North America. That was basically what
3 happened in that outbreak that Dr. Groshkopf discussed
4 in the VE presentation.

5 These were all these viruses with D53G in
6 addition to the Darwin/6. They have the D53G and the
7 157I. Darwin/6 is a very advanced virus that does
8 contain the 156S substitution, which is common in most
9 of the viruses circulating now. Then you can also see
10 the D53N group; that's the lighter green with 96N,
11 156S, and I192F. And they are from western Europe such
12 as the Netherlands and Sweden and in the South America
13 and Brazil.

14 The clade 1a viruses are circulating in
15 Africa, Côte d'Ivoire, Ghana, so, in Western Africa, up
16 in Nigeria, but also in Ethiopia more towards the east
17 there. So then, we have those viruses circulating
18 there, and the clade 1b viruses were only sporadically
19 identified in those countries listed. I won't walk you
20 through that.

21 So now, where are these substitutions that

1 this genetic difference is in code? What I'm showing
2 you here is on the left the Cambodia/E0826360. This is
3 the Northern Hemisphere 2021/'22 vaccine prototype --
4 so, you can still get this vaccine. There may still be
5 time; we could have a late flu season -- and the
6 Southern Hemisphere 2022 prototype, the Darwin/6 which
7 is also the recommendation for our Northern Hemisphere
8 2022/'23 season.

9 The one thing that you should be able to
10 appreciate is that they share a lot of the same
11 substitutions. So, all of those red dots that you see
12 on the molecule represent changes from the prior
13 vaccine A/Hong Kong/45/2019. And many of these are
14 very important antigenic sites. Sites A and B at the
15 tip or head of the molecule, those are the kind of
16 light colored -- the kind of light tan color and the
17 light green color. So that's showing you the epitopes.
18 And then the light yellow is a different epitope and
19 blue is a different epitope and the dark blue is a
20 different epitope.

21 But many of these substitutions such as 137S,

1 186S, 135T, these are very important epitopes in the
2 molecule, and they're shared between Cambodia and
3 Darwin. The difference between these Darwin-like
4 viruses, which are the 2a.2 versus the 2a.1, are the
5 additional substitutions at 156S. A big one is that
6 one at 159N. And another large change is the T160I,
7 which has that little star symbol next to it. You can
8 see where it is in the 180-degree rotation right at the
9 tip of the molecule.

10 And that position leads to a removal of a
11 glycan at position 158. So, a glycosylation site at
12 158, and that's a very important antigenic
13 distinguishing feature of H3 viruses that first emerged
14 in 2014 and has continued since that time. So that
15 represents a change.

16 So here this shows the summary of the
17 antigenic analysis of the antigens recommended for the
18 Northern Hemisphere 2021, again Cambodia. And you can
19 see now these viruses can now be hemagglutinated again,
20 and that's partly because of that T160I and the 158
21 change now allows it to bind red blood cells in vitro,

1 and we can use hemagglutination inhibition assays as a
2 surrogate for virus neutralization. And two of the CCs
3 did that quite a bit: the Francis Crick Institute,
4 which is FCI; and VIDRL. And you can see their total
5 data here with only 18 percent considered like against
6 the cell antigen and 82 percent considered low, so an
7 eight-fold or greater to the homologous titer, and the
8 egg was a little bit worse where you had only six
9 percent considered like.

10 Going down to the neutralization assays, you
11 can see the totals here where about 18 percent are
12 considered low. So very consistent with the HI assays
13 -- I mean, 18 percent considered like and 82 percent
14 considered low.

15 Now moving into the Darwin/6 cell analysis.
16 It's really the opposite where 85 percent are
17 considered like in the HI assay in the antisera against
18 the cell antigen. And the antisera to the egg antigen,
19 64 percent are considered like. Not too bad for an egg
20 antigen. And by virus neutralization, it's actually a
21 little bit better.

1 This shows you the antigenic cartography.
2 Again, the 2a.2 viruses are antigenically distinct from
3 the 2a.1 viruses and the 1b viruses. And so, this is a
4 little bit high-level view where the 2a.2 viruses are
5 the brown and green dots up in the top. So the key is
6 right here. I'm sorry there's so many colors, but we
7 were really trying to determine if the 156S versus the
8 156S with 53G -- which is the lighter brown color --
9 and the 156S with the 53N -- which is the olive-green
10 color -- were antigenically distinguishable.

11 And what you can see is that they all kind of
12 intermix in this antigenic map indicating that there is
13 not strong antigenically distinguishing features by the
14 addition or subtraction of these amino acid groups.
15 And then with the Cambodia is this kind of orange
16 circle down near the bottom. You can't see the label
17 very well, but it says CA/20 cell. That's the large
18 orange circle, so it shows you where the Cambodia is;
19 and the bright fuchsia circle shows you where the
20 previous vaccine Hong Kong/45 is. So, you can see that
21 they're antigenically distinguishable from the Darwin-

1 like viruses or the 2a.2 viruses.

2 And those bright green ones off to the left
3 where it shows KS17, that's the Kansas antigen from
4 2017, and you can see where that sits. And so, there's
5 been some convergent evolution between that group of
6 viruses and the most recent viruses. And you may
7 remember that's the virus that we had to delay the
8 vaccine decision for to make that vaccine candidate.

9 So, this shows you a closer view of both data
10 from using HINT, which is High-contrast Imaging
11 Neutralization Test. It's a new technique we developed
12 at the CDC that can really distinguish small antigenic
13 features and a closer view of the work from the HI data
14 in Crick at the London CC.

15 And so, you can see how the data really looks
16 quite similar between the two groups and that we don't
17 see the same huge distinguishing features between the
18 various flavors of the 2a.2 subclade viruses.

19 Now here's looking at the human post-
20 vaccination serum. Multiple serum panels do show
21 reduced reactivity. Remember, they were vaccinated

1 with a 2a.1 virus against the 2a.2 viruses, so they are
2 statistically -- we can see in the dark orange colors
3 as you get in that orange bar down there. That's where
4 we have significant statistical difference where they
5 would be considered inferior. The vaccine antigen may
6 be considered inferior against those particular
7 antigens.

8 So, you can see a stark contrast here, but
9 what you'll also see, which is probably important to
10 note is that the newer 1a virus like the Togo/771 is
11 well protected. So, people that would be potentially
12 infected by that virus would be better protected with
13 the current vaccine, and the 1b viruses we're still
14 getting great cross reactivity, so back boosting
15 against those.

16 This slide now goes back through those bubble
17 plots, and I just want to focus you on the 2a.2. So,
18 we selected last year a 2a.1 virus, which were really
19 the viruses that we had available and were the new
20 emerging group. And you can see, again, in the
21 children, it doesn't work so great in the very young 6

1 to 35 months old, very similar to what we saw with the
2 H1.

3 We'll now just go to the second set of rows.
4 The Flucelvax set of columns; you can see a forward
5 boost. So, you can see both a back boost -- so
6 Cambodia you can compare that SIAT column, so that's
7 the cell-based Cambodia. It has a geometric mean titer
8 of 171 post-vaccination. So that improved to a
9 geometric mean titer of 30.

10 And, if you look across that column, you can
11 see that against the total 771, which is a different
12 variant, it has a geometric mean titer of 166 -- so not
13 bad -- and 75 percent of them now are above 40. The
14 same is true of Hong Kong/45 where you get a little bit
15 higher titers. So that's what we call our back boost.
16 It's boosting into the older viruses with a higher
17 geometric mean titer than the homologous antigen. So,
18 it's 219 instead of 171. And then as you move into
19 this antigenically advanced group -- clearly advanced
20 based on the ferret data, the Darwin/6-like viruses --
21 we still have a GMT of 89 and 70 percent considered

1 above or equal to 40.

2 Basically, the same numbers for these more
3 advanced viruses such as the Maryland/02 with the 157I
4 and D53G substitutions. And the Alaska/01
5 representative, which is that other group, the D53N and
6 186S. So, we try to pick these new emerging groups for
7 analysis in the closed vaccination serologic analysis.

8 I won't walk you through this slide. I think
9 it's basically the same. We saw with adults,
10 vaccination increased titers to HA clade 1a, 1b, 2a.2.
11 And remember this is a 2a.1 vaccine. So, we saw both
12 back boost and a forward boost against recent 1a,
13 multiple 2a.2 variants, and the titer and forward boost
14 reduced in older adults and elderly.

15 So, I did want to -- maybe I'll point that
16 out. If you look at the pre and post here as you go
17 down this column into the elderly, you don't get as
18 strong of a forward boost as you see with the adults,
19 both in Flucelvax, and Flublok, and the IIV4.

20 So, to summarize the H3N2, in many countries,
21 areas and territories reporting Influenza A(H3N2)

1 subtype predominated. And most countries in Europe,
2 North America, Middle East, South America, and some
3 countries in Africa -- they are listed there -- where
4 we saw H3N2 predominated.

5 The phylogenetics of the HA show that the H3N2
6 virus is circulating in this period really belong
7 primarily to a variety of subclades -- the 1a, 1b,
8 2a.1, and 2a.2 -- with the most recent viruses being
9 this 2a.2 HA clade that's predominated and continued to
10 diversify into two main subgroups that we'll probably
11 be talking about in the future. Hopefully, one of them
12 will die. The D53G subgroup with 156S and 157I; or the
13 D53N subgroup with N96S, which affects another
14 glycosylation site, and N156S and I192F, which is right
15 up in the head of the hemagglutinin molecule.

16 The antigenic characteristics. All the 2a.2
17 viruses were antigenically distinct from 2a.1 and 1a,
18 1b viruses. And this ferret antisera really delineates
19 that. It's here for posterity. We go into the human
20 serology studies; however, post-vaccination GMTs were
21 significant when reduced against those 2a.2 viruses.

1 And viruses with the HA and the 2a.2 subclade, that
2 were either the 53N or 53G, all showed similar
3 reactivity patterns. So, what I'm saying there is they
4 were difficult to distinguish antigenically at this
5 time.

6 And nevertheless, the 2a.1 vaccine provided
7 forward boost against 1a and 2a.2 viruses, and often
8 the majority of individuals had titers greater than 40.
9 And so that's a plug for why we get vaccinated even if
10 there's an antigenic quote distinguishing virus that's
11 emerged.

12 And antiviral susceptibility genetic and/or
13 phenotypic testing showed that only one of a thousand
14 viruses -- more than 1,000 -- 1,023 -- collected after
15 September 2021 showed reduced inhibition to the
16 neuraminidase inhibitors and even better shape in the
17 baloxavir. Out of 962, none showed evidence of reduced
18 susceptibility.

19 Okay, so now it's time to talk about the
20 Influenza B viruses. This shows you the number of B
21 viruses detected by the GISRS, again, the yellow bar

1 showing you the 2021 flu season -- or year I should say
2 -- and, again, beginning to see a subtle increase
3 beginning as early as Weeks 35 but just really
4 gradually increasing all the way into Week 52 and then
5 declining from that point in the red bar, as you can
6 see -- red line.

7 This shows you the Influenza B viruses
8 ascribed to their lineages, the numbers and the
9 percentages where basically -- I'll just give it to you
10 in a nutshell -- virtually all the viruses detected
11 were B/Victoria viruses. And there were some where the
12 lineage was not determined.

13 This slide shows you the activity. And as I
14 mentioned early on, China didn't have activity in other
15 viruses, but they had a lot of activity in Influenza B,
16 along with Madagascar. And so, a lot of the data for
17 this B decision came out with China National Influenza
18 Center, which is also a WHO Collaborating Center.

19 Now, we're looking at the high-level
20 phylogeny, 50,000-foot view again, showing you how the
21 B viruses have evolved over the years, and the first

1 set of big drift variants came as the V1A.1. As you
2 start falling from the top of that tree, you can look
3 to the long black bar about a third of the way down.
4 That was called the double deletion variant that had
5 the deletion of the amino acids 162 and 163 in the
6 hemagglutinin molecule.

7 And then came the triple deletion variants
8 which is the very long bar going down. You can see now
9 in the very first columns where there's tick marks, you
10 can see the blue and the green and red, small red tick
11 marks. That is the triple deletion viruses. The first
12 virus is circulating there, and that is represented by
13 the Washington/02 virus that was in our vaccine, for
14 example. And they continue to evolve.

15 So, what's come through the bottleneck of
16 COVID is these 1A.3a.1 and 3a.2 viruses. And so, you
17 can see all those red dashes and a few orange dashes
18 there indicating China, Africa, and very few blue and
19 green in Europe and North America. And so, in China,
20 they had both these 3a.1 viruses, and they had 3a.2
21 come in later and begin to displace the 3a.1.

1 This is a close-up view now of the
2 phylogenetic tree, looking closer now at the top of
3 this tree, the 3a.2 viruses. We can see at the very
4 top of this tree all of those red dots that don't have
5 any -- they're vertical, that's called monophyletic.
6 So that means all those viruses are virtually -- their
7 hemagglutinins are virtually identical to each other.
8 It's not even a nucleotide different.

9 So that's just really an epidemic virus doing
10 very well in the community. And a recommended vaccine
11 prototype is labeled up near the top of that tree,
12 B/Austria/1359417. Both the egg and the cell are
13 nearly identical, and they're both shown on the tree
14 there. So that's the egg prototype and the cell
15 prototype. They do have minor distinguishing
16 characteristics.

17 That's the main thing I want to focus you on
18 the 3a.2s. And then the 3a.1s are about the mid-level
19 of the tree, and they're represented by that B/Sichuan-
20 Jingyang virus. And that will be in the serology study
21 that I'll show you later, along with as we go up some

1 new diverse 3a.2 viruses that have this T182A/197E
2 that's boxed like B/Henan-Xigong. I'm sorry, I can't
3 pronounce that correctly.

4 Oh, I want to point out where Washington/02
5 is. So, the current Northern Hemisphere cell prototype
6 is this Washington/02. It's down here in the base of
7 the tree. So, all the viruses really are derived from
8 viruses like Washington/02, and they're in the 183
9 group. And that was our Northern Hemisphere prototype
10 that we got this year.

11 So, looking at the viruses characterized
12 during the last three reporting periods, you see that
13 there's just been very little B circulation after the
14 2019/2020 season except in China where you can see the
15 2021-to-2022-time frame. There was more than 1,600
16 viruses characterized, so many more than that
17 identified.

18 Again, this is a high-level view of what the
19 analysis of the antigenic analysis of the viruses looks
20 like. So, this is antisera against either the
21 Washington cell recommendation or the Washington egg

1 recommendation. And you can see that in the United
2 States, for example, at the CDC, 68 percent were still
3 considered Washington cell-like. But the CNIC, which
4 is the China National Influenza Center, only 38 percent
5 were considered like. And so it's really showing you
6 the geographic differences between what's circulating.
7 And 62 percent were considered low there. Overall, the
8 totals show that only 38 percent are considered like
9 Washington and 62 percent considered low, really
10 illustrating that globally antigenic drift is
11 happening. And then if you look at the egg-based
12 vaccine, it's actually quite similar with 33 percent
13 and 67 percent respectively.

14 Now, looking at the new recommendation for the
15 Southern Hemisphere 2022 and the WHO recommendation
16 that we are considering today, the B/Austria/1359417
17 virus, you can see that 88 percent are considered like
18 and only 12 percent are considered low. And, again,
19 you can see some geographic difference there with the
20 CDC seeing a little bit higher percentage considered
21 low to that B/Austria virus antisera. And a very

1 similar phenomenon with the egg, the egg actually looks
2 one percent better considered like -- so I'd call that
3 the same -- and 11 percent considered low.

4 Again, showing you the antigenic cartography.
5 Now this is coming from data from the collaborating
6 center in Beijing that produced all this data. And so,
7 again, you can see these various HA subclades. The
8 3a.2 and 3a.1 viruses are antigenically distinct from
9 the clade 3. And so, if you really look at the green
10 viruses versus the yellow there to see that, how far
11 apart they are and where that Washington/02 cell and
12 egg are shown.

13 And then, also, where viruses, even in China,
14 that were circulating that were more like Washington.
15 But you can see how they had many more viruses that
16 were the 3a.1 or 3a.2 viruses. And you can see where
17 the B/Austria egg virus sits amongst all of those.
18 It's that big oval-shaped dot.

19 And so, you can see that the various subgroups
20 are antigenically close related, and they form
21 overlapping clusters. So, all the 3a.2 viruses really

1 are forming overlapping groups, again, so the different
2 colors of light green there. There's an olive-green
3 color showing you the 3a.2s with the 197 substitution
4 and a very hard to probably distinguish on your
5 computers, but an in-between green color, a little bit
6 darker than the light, light green, is the 122Q.

7 Again, so we're seeing some genetic diversity
8 that's not equating to antigenic features that we can
9 tell yet. And then in darker green are the 3a.1
10 viruses that circulated primarily only in China. And
11 you can see they form a distinguished -- a related, but
12 antigenically distinguishable group from the 3a.2
13 viruses.

14 Now, looking at the post-vaccination in humans
15 serum analysis. Now, remember in the Northern
16 Hemisphere, people were vaccinated with the
17 Washington/02, which is the older V1A.3 virus. You can
18 see that even in the very young pediatric population,
19 while the titer was low, it was pretty good cross-
20 reactivity even into the 3a.2 group.

21 Looking at that Austria-like virus, that's the

1 new vaccine prototype, but we did see some reductions
2 again once you get to that further involved Henan-
3 Xigong virus that had the 122Q, for example, or the
4 Maryland/01 virus that had that one 127T and 197E that
5 I pointed out on the tree. But then when you get into
6 the older populations, you can see great cross-
7 reactivity across these two different clades or forward
8 boosting would be another way to put it. I'm not going
9 to bother showing you the bubble plots for that. The
10 statistical analysis shows it.

11 If we go to the B/Yamagata lineage viruses.
12 These are the unseen viruses so far. So, B/Yamagata
13 lineage virus detections have really been very sporadic
14 and occasional reported to the FluNet system within WHO
15 and only 13 positives reported. But none of those had
16 been confirmed by WHO Collaborating Centers. So, we
17 request these and try to grow them or retest, and we
18 have not confirmed any of those viruses yet. And no
19 viruses of this lineage -- B/Yamagata -- have been
20 available for analysis during this period, so that will
21 save us some time. I won't show you data from them.

1 No B/Yamagata/16 viruses were detected or
2 confirmed so this is for future considerations since
3 March 2020. And it's unclear at this point if this
4 lineage are truly extinct and hence, for the 2022/'23
5 Northern Hemisphere quadrivalent influenza vaccines, a
6 B/Yamagata lineage virus is still recommended. The
7 recommendation hasn't changed from the B/Phuket virus.

8 The WHO GISRS in consultation with other
9 parties will reconsider the situation in about a year
10 as to the necessity for including B/Yamagata lineage
11 viruses in influenza vaccines.

12 Only B/Victoria lineage viruses were detected,
13 so as part of our summary for Influenza B here, the HA
14 phylogenetics of the B/Victoria lineage viruses, nearly
15 all the HA genes belonged to subclade 1a.3 that has
16 deletion of residues 162 through 164 and an additional
17 K136E substitution. So, everything's really derived
18 from that type of a virus, which B/Washington/02 is a
19 representative of. We've seen further evolution of
20 this HA gene to the 3a, which include these additional
21 substitutions: the 150K, 184E, and 197D. And that's

1 really what came through the COVID bottleneck were
2 these 3a-like viruses. And they've continued to
3 evolve, and two subgroups have emerged. The 3a.1,
4 which has these additional changes at 220M and 241Q.
5 We did discuss this last VRBPAC meeting. They've just
6 had kind of evolved, these two groups.

7 And then the 3a.2, which have this 127T, 144L,
8 and 203R, which were seen more globally: Asia, Africa,
9 Oceania, Europe, and North America, although with
10 limited circulation in those places in contrast to
11 China which had heavy circulation of Influenza B. What
12 China was also able to delineate as part of the
13 Southern Hemisphere strain selection was that the 3a.2
14 virus started to out compete the 3a.1 viruses. And so,
15 it started to displace those in China and have
16 continued to do so. The 3a.2 viruses have further
17 genetic divergence, and they have additional
18 substitutions encoded in viruses from different
19 geographic regions.

20 However, those were not antigenically
21 distinguishable. And so, I'd like to remind you about

1 the Yamagata. We haven't really seen any, although 13
2 were reported and no viruses of this lineage have been
3 available for analysis.

4 And I'd like to acknowledge all the other WHO
5 Collaborating Centers, the entire GISRS of over 150
6 laboratories that make this system function, our
7 partners at the University of Cambridge who do their
8 large 50,000-foot phylogenetic trees and the antigenic
9 cartography that I showed you.

10 The essential regulatory laboratories are key
11 partners in this, like FDA, TGA, NIBSC, the U.S.
12 partners, the Association for Public Health
13 Laboratories. Of course, the United States Air Force
14 School of Airspace Medicine, they are very great
15 partners; we have collaborated with them. In fact, the
16 Maryland/02 that you saw used in our serology assays
17 came from an outbreak in Maryland in a military
18 location, and we were able to obtain that very early
19 before even the college campuses had outbreaks. But
20 thanks very much. The Naval Health Research Center is
21 also a collaborating partner in that group.

1 (audio skip) or -- because the factors looked good, but
2 I don't know.

3 **DR. DAVID WENTWORTH:** Yeah, very, very
4 interesting question and very important question. And
5 because the HA is the primary target of all of our
6 vaccines, although we do a lot of neuraminidase
7 phylogenetic analysis, and some we did antigenic
8 analysis of the neuraminidase this time, I left it out
9 because of time. It's three or four viruses we have to
10 cover in some detail, so I didn't show the
11 neuraminidase data, but we do look at it.

12 The neuraminidases of the viruses that are
13 circulating are very closely related to the Darwin/9
14 egg neuraminidase and pretty close to the Darwin/6 egg
15 neuraminidase. So, it's a great point, but we haven't
16 seen a lot of evolution in the neuraminidase that would
17 suggest that's part of the evasion. I mean, it's
18 evolved from the earlier influenza viruses, but there's
19 some pretty important sites that affect a glycosylation
20 that exists in the Cambodia. The older vaccines, all
21 the 2a viruses have that, whether the 2a.1 or 2a.2. So

1 that we know is an important antigenic characteristic
2 shared by both vaccines. So that's good. And so that
3 doesn't really explain, like the VE data that you saw
4 earlier.

5 I would point out -- I mean, I would think
6 that that VE data is critical and we have to pay
7 attention to it and it is a self-check on our
8 selections that we make prior to knowing what's going
9 to happen. I think that the serology data is a more
10 direct analysis of what happens when you get
11 vaccinated. And so that's why we've added it to the
12 VRBPAC in more detail over the past couple years in
13 response to the Committees' questions. And I took such
14 a long time going through it today because, in general,
15 people don't realize the good.

16 If you look at those pre-titers, those blue
17 circles, there's no hope. And if you look at the red
18 circles or orange circles, many people are pushed above
19 40 which is a correlate of protection. So, there is
20 this dichotomy between what the VE tells you and what
21 the serum tells you, and neither is right. So, there's

1 some that will be above 40 that wouldn't be protected.
2 Some might be 40 and below and still protected, and so
3 it's a very difficult question.

4 But with regards to the VE, we didn't have
5 what we call a lot of virologic pressure. Even the
6 little peak of H3 we had this year was small in
7 comparison to previous years. So only getting up to
8 four or five percent positivity rate when some years
9 it's 18 percent. Right, so when that infection course
10 is very low, it challenges a negative test design VE to
11 really produce strong data because you don't have
12 enough infection force. And personally, I read that VE
13 data as the range that's lifted there. It's either
14 minus 24 to 39 or this point estimate of 14. When it
15 crosses the zero, it's really statistically
16 insignificant.

17 And so, if you looked at it instead of the
18 point estimate as the range, what you really are saying
19 is that we're not super confident in that point
20 estimate. It's crossing the zero, and it's going up.
21 It could've been 43 or whatever the top part of that --

1 I'd forgotten what Dr. Groshkopf showed -- but also
2 that's preliminary data in part because they haven't
3 gotten all the data in from the people that were
4 infected in a very weak influenza season. Sometimes,
5 if H3 peaks very early and we have a lot of virus
6 around, it's much easier to get a strong point estimate
7 with a narrow confidence interval around VE.

8 And I do think the U.S. armed forces were able
9 to do that and have a tighter confidence interval that
10 is above the zero and do have a little bit better point
11 estimate. So, I think in the U.S. VE network it went
12 from somewhere from minus 28 to 43, right? So, it
13 could be as good as 43 or as terrible as 0 because
14 there's no such thing as negative VE, right?

15 Also because this is a public meeting, I want
16 to point that out. That negative number does not mean
17 that the vaccine causes more flu, okay. That negative
18 number is the statistical analysis negative number, and
19 when it crosses the zero, it really makes us nervous
20 about the point estimate -- not nervous, uncertain
21 about the point estimate. We're trying to show you in

1 that range the uncertainty that we have in the
2 analysis, and Dr. Groshkopf did a great job showing
3 all the things that could affect it, including the
4 unusual COVID pandemic situation where we have health-
5 seeking behavior that is much different than normal.
6 So, probably a lot of caveats on the VE.

7 **DR. HANA EL SAHLY:** Probably a lot of the
8 testing in the outpatient also strictly tested for
9 SARS-CoV-2 and not the multiplex.

10 Thank you, Dr. Wentworth. I do not see any
11 raised hands. So, if we don't have any additional
12 questions or comments, we will take a break.

13 **DR. DAVID WENTWORTH:** That either means it was
14 not very clear or it was very clear. I don't know. I
15 hope it was clear. But in the end, we did discuss at
16 the outset alternatives. I don't want to make this
17 seem like it's a fait accompli analysis. There is
18 always the option if the Committee feels very strongly.
19 We won't be able to necessarily answer a question
20 today. I might have to go back. We might just set up
21 another meeting so I could give you some alternative

1 candidates. But we always are looking at that. And as
2 Dr. Weir mentioned, the U.S. does have fairly strong
3 representation in the WHO committee.

4 There was one season very long ago where the
5 VRBPAC chose to choose one of the strains differently,
6 for example. And the other thing we've done as a
7 committee for the WHO -- I kind of mentioned it in this
8 talk briefly -- but just for historical reference;
9 nobody felt comfortable with the decision on the H3
10 virus at the time the decision had to be made. And
11 therefore, the entire WHO committee postponed the
12 decision until we had more data on a very recently
13 emerging H3 virus and were able to successfully get a
14 candidate vaccine virus and distribute it globally with
15 only a month delay.

16 That did cause some manufacturing delays, and
17 it's important that manufacturers don't take lightly to
18 postponing that. But just for everyone's awareness, if
19 we are uncertain and we have to, we will postpone a
20 decision.

21 **DR. HANA EL SAHLY:** Okay. Thank you. I have

1 now two members with questions, Dr. Janes and Dr.
2 Portnoy. And we will begin with Dr. Janes.

3 **DR. HOLLY JANES:** Thank you, Dr. Wentworth. I
4 really appreciated the care and time that you took to
5 go through this today. I wanted to follow up on your
6 discussion of the limitations and interpretability of
7 the preliminary VE estimates versus the immunological
8 and phylogenetic data that you've presented. This
9 Committee is always presented with these preliminary VE
10 estimates, and they're especially limited in quantity
11 and quality this year given the pandemic.

12 Does any set of this team go back at the end
13 of the year once the final VE estimates are in and
14 correlate what the VE estimates with what was seen
15 based on the immunology and the phylogenetics to help
16 us prioritize and interpret the relative merits of
17 these different data types? I mean, after all, I think
18 we'd all agree that the VE estimates are what we care
19 about. It's just that they're limited in precision,
20 especially this year and in general, always limited in
21 precision when we look at subgroups and vaccine type

1 and so on.

2 **DR. DAVID WENTWORTH:** Yes. Sorry, every time
3 I turn my microphone on my phone talks for a while.
4 So, yes, this is done. So, there's two things that
5 happen. One, a full VE estimate from a season is
6 nearly al- -- if we have a strong enough season -- is
7 nearly always published in a variety of different
8 journals. So that's done. The cohort that we get the
9 vaccine serum from and the VE data are completely
10 separate. So that's a little tricky, but we definitely
11 look at the trends.

12 Third, when we have a special study such as
13 what Dr. Groshkopf mentioned with the campus outbreak,
14 there they can do a combination, and there's still more
15 and more analysis happening with that outbreak, I
16 think, that we'll be looking if possible, having serum
17 from individuals. Not only were they vaccinated, but
18 how well did they respond to the vaccine? That is one
19 of the challenges of the influenza vaccine. It's very
20 safe, not very reactogenic, and so there are a number
21 of people that just don't mount a strong response once

1 they are vaccinated. So that does happen.

2 But usually, when would it -- I guess I would
3 anticipate that young adults in the college-age setting
4 probably would've had an okay response. Clearly,
5 there's -- I think within that paper or in some
6 preliminary data, there isn't strong neutralization
7 titer among those vaccinees against the Darwin/6-like
8 viruses that circulated in that location. I'm not sure
9 why I'm not telling you which college campus it was,
10 but I think it's published. But I don't know if that's
11 okay, so I'm just not going to mention that. But it's
12 just a college campus location. It's a big campus, big
13 college.

14 So, yes, we do. The long-winded answer was
15 that. But the short answer is, yes, we do try to
16 correlate those things when we can, and that's one of
17 the advantages of doing an EPI8 and working with public
18 health partners that are so great on those studies.

19 **DR. HOLLY JANES:** Thank you. I guess just to
20 follow up on that, I wonder if it's worth considering
21 if that would be appropriate to present to us at some

1 point. It would obviously apply to past years when the
2 final VE estimates were in. But I think it would be
3 informative for interpreting the current year's
4 immunological phylogenetic data.

5 **DR. DAVID WENTWORTH:** Thank you.

6 **DR. HANA EL SAHLY:** The last question is from
7 Dr. Portnoy.

8 **DR. JAY PORTNOY:** Oh, good. I always like to
9 get the last word. No, your presentation was amazingly
10 clear and somewhat overwhelming. I think that may be
11 part of why we aren't getting a lot of questions. But
12 thank you for that presentation, it was really helpful.

13 My question involves the wisdom of including
14 the B/Yamagata strain in the vaccine. We only have
15 room for four strains, and one of them is a strain
16 that's essentially extinct. My understanding is that
17 the intent is to give it long enough so that it
18 actually becomes extinct. Only one virus in history
19 has actually undergone that, and that's smallpox.

20 And I just question the need to do that
21 because there were no strains isolated this last year.

1 Wouldn't it be more prudent to maybe include the A5.1
2 along with the A5.2 just to get more complete coverage
3 as opposed to using up one of the four available slots
4 for the B/Yamagata? Do you have any thoughts about
5 that?

6 **DR. DAVID WENTWORTH:** Yeah, thank you very
7 much for that question. And I think it's an important
8 question. And there's a couple of things going on that
9 I'll try to address. One, there is a large iceberg of
10 influenza. It's a simple way to think about it. B
11 viruses, A viruses, the viruses in animal reservoirs,
12 luckily with B viruses, they primarily only infect
13 humans. So that's one important difference from A
14 viruses. And so, there is potential that it is
15 extinct, and in part, it makes a lot of sense because
16 the first thing that happened if you think about the
17 Influenza B viruses is we had a double deletion variant
18 which swept the world and really stimulated immune
19 responses that likely cross-reacted with the
20 B/Yamagatas.

21 And then, subsequent to that, we had a triple

1 deletion B/Victoria variant that also did the same
2 thing. And then, right after that, SARS coronavirus
3 happened where we had all the mitigation associated
4 with preventing the COVID-19 -- you know, mitigating
5 the COVID-19 pandemic. So, all three of those could
6 easily have strongly contributed to the kind of
7 extinguishing of the B/Yamagata lineage.

8 However, as I mentioned, there's a very large
9 iceberg. Our surveillance is not complete in any one
10 country, let alone the world. And so, there could be
11 small pockets of B/Yamagata still circulating that
12 could emerge, and we want to be cognizant of that and
13 include the B/Yamagata in the vaccine.

14 And then the second kind of related but
15 unrelated part/answer to that question -- and I can
16 turn it over to the FDA -- is a regulatory question.
17 And so right now the licensed vaccines are
18 quadrivalent, and they have one of each of the
19 components: A(H1N1)pdm09, A(H3N2), B/Victoria, and
20 B/Yamagata. You can't just substitute another H1 or
21 another H3 into that licensed vaccine.

1 So there needs to be a lot of work done in
2 probably pre-clinical and clinical settings to
3 understand reformulating the vaccine like that and
4 putting two of H -- I think most of us are discussing
5 putting two H3s. H1s induce pretty good cross-
6 reactivity. H3s are a little more challenging, and so
7 it would be really -- to make my life a lot easier if I
8 could pick two H3s. I could tell you that. The whole
9 Committee would be happy.

10 So that is something that I think a lot of
11 researchers are starting to investigate. While we
12 wait, basically time will tell if that B/Yamagata
13 lineage is truly extinguished. As I said, we had 13
14 detections. Most of them were very high CT, so in PCR,
15 they were PCR detections. So, they had very small
16 amounts of virus genome in that detection, and they
17 could not be isolated.

18 And the other confounding piece is in the live
19 attenuated vaccine -- which is quadrivalent -- there is
20 B/Yamagata lineage. And so sometimes, someone may get
21 the live attenuated vaccine, and then, for whatever

1 reason, they're tested maybe a few days later and they
2 come up positive for Yamagata. So, some of those might
3 be live attenuated detections and some of them might be
4 real but so low we can't isolate a virus.

5 And so, just picture an iceberg and think
6 about there's a lot under the water that we don't see,
7 and our only real test will be time to know that it's
8 fully extinguished. And then potentially setting up
9 very in-depth studies where you go look specifically,
10 like very deeply, for B viruses and Yamagata lineage
11 viruses.

12 **DR. JAY PORTNOY:** Great. Thank you.

13 **DR. DAVID WENTWORTH:** A lot of people
14 considering that open window of 15 micrograms of
15 antigen that could be different than a B/Yamagata.

16 **DR. JAY PORTNOY:** And I agree with you. I
17 think that the FDA or whoever makes those decisions
18 ought to reconsider reformulating the vaccine to
19 possibly include more or different strains. But thank
20 you very much.

21 **DR. DAVID WENTWORTH:** Yeah. I think it would

1 have to be probably led by the companies, and they
2 would have to petition the FDA, here's our data and
3 this is why we think we can do it. But I can turn it
4 to them.

5 **DR. JAY PORTNOY:** Thank you.

6 **DR. HANA EL SAHLY:** And, Dr. Weir, is going to
7 probably try to shed light on this question.

8 **DR. JERRY WEIR:** Dave, you gave a great
9 regulatory answer. I'm not sure I have to add much.
10 It is true that any changes like that were being
11 discussed would have to be chan- -- the manufacturers
12 would have to change their licenses, and that would
13 require data. Of course, it can be done. But, yes,
14 you would have to -- just like when we added the fourth
15 strain that required data from each individual
16 manufacturer to change their license.

17 The only thing I do want to add is that all of
18 the manufacturers are still licensed to produce a
19 trivalent. So, if for some reason there was a
20 recommendation coming that said there really is no
21 point in adding a fourth strain, they would not have to

1 change licenses to go back and produce a trivalent.
2 Their license is still in effect for that. But, yes,
3 data would be needed and it can be done and it could be
4 done. But it would require data and an updating of
5 their license. Thank you.

6 **DR. HANA EL SAHLY:** Hmm. All right. Thank
7 you all. I turn the meeting over now to Michael
8 Kawczynski for the break.

9 **MR. MICHAEL KAWCZYNSKI:** All right. Thank
10 you. And thank you for all the speakers and I'll say
11 our first morning portion of today's event. Looking at
12 the time, we're going to take a short ten-minute break,
13 so we will reconvene at 11:25.

14 **[BREAK]**

15

16 **DoD INFLUENZA SURVEILLANCE AND MID-SEASON VACCINE**

17 **EFFECTIVENESS**

18

19 **MR. MICHAEL KAWCZYNSKI:** All right, and
20 welcome back to the 171st Vaccines and Related
21 Biological Products Advisory Committee Meeting. This

1 one's on influenza. I'm going to hand it back over to
2 our chair, Dr. El Sahly, go ahead, take it away.

3 **DR. HANA EL SAHLY:** Thank you, Michael, and
4 welcome back. So, next on our agenda, Dr. Courtney
5 Gustin. Dr. Courtney Gustin is from the Armed Forces
6 Health Surveillance Division, Global Emerging
7 Infectious Diseases Surveillance Branch. And, Dr.
8 Courtney will give us an overview of the DoD influenza
9 surveillance and the (audio skip), Dr. Gustin.

10 **DR. COURTNEY GUSTIN:** Good morning. My name's
11 Lieutenant Commander Courtney Gustin and I'm part of
12 the Defense Health Agency's Armed Forces Health
13 Surveillance Division. I'm going to be presenting the
14 results from the Department of Defense Global
15 Respiratory Pathogens Surveillance Program and for the
16 partners that contribute to this important effort on an
17 annual basis.

18 Today I'll be presenting data on the 2021-2022
19 influenza season from our influenza surveillance
20 network. Including an overview of the past three years
21 of surveillance data with a snapshot of what's taken

1 place during the pandemic. Included here will be
2 surveillance data from our partners in North America,
3 South America, Europe, the Middle East, Africa, and
4 Asia. As those other contributors, are analyses this
5 year will be very limited in comparison to previous
6 years due to both the low number of influenza cases
7 captured through our surveillance program over the last
8 several months, and pandemic prevention efforts.

9 I will provide a summary of phylogenetic
10 analyses developed by the U.S. Air Force School of
11 Aerospace Medicine, or USAFSAM, and I'll share data on
12 antigenic characterization for the season from the
13 Naval Medical Research Center, or NMRC. And, in
14 addition, I'll present mid-year estimates of vaccine
15 effectiveness developed by the Armed Forces Health
16 Surveillance Division Epidemiology and Analysis Branch.
17 Finally, we'll review DoD's vaccine strain
18 recommendations.

19 I'll start off with an overview of influenza
20 surveillance within the DoD. Flu surveillance is
21 included as part of the DoDs Global Respiratory

1 Pathogens Surveillance Program, which is managed out of
2 the Global Emerging Infection Surveillance, or GEIS,
3 Branch at the Armed Forces Health Surveillance
4 Division. The GEIS branch is a DoD asset dedicated to
5 the surveillance of infectious disease primarily, but
6 not exclusively, within the military community. Our
7 influenza surveillance program extends to over 400
8 locations in 30 countries through the work of DoD
9 laboratories across the globe.

10 In addition to monitoring U.S. military
11 personnel, our partners have relationships with foreign
12 governments, including ministries of health, ministries
13 of defense, and academic institutions. Which provide
14 disease surveillance data on local, national
15 populations. Our laboratories have extensive
16 characterization capabilities, including cell culture,
17 PCR, and sequencing capabilities. On average,
18 approximately 30,000 respiratory samples are collected
19 and analyzed each year within our network. We also
20 have access to extensive health records for active duty
21 military personnel, which are typically an important

1 source of data for monitoring influenza within DoD and
2 conducting vaccine safety and effectiveness studies.

3 I'd like to briefly show where GEIS-supported
4 influenza surveillance is active. The GEIS network is
5 spread across all six geographic combatant commands and
6 multiple laboratories conduct influenza surveillance
7 routinely. One of the core GEIS laboratories, USAFSAM,
8 has a particularly wide geographic footprint. And
9 surveillance for influenza across many sentinel sites
10 in the US1, Europe, and locations in the Indo-Pacific
11 region. Testing for influenza declined significantly
12 in 2020 and continued that trend into 2022 in the midst
13 of the COVID-19 pandemic. Over the next several slides
14 I'll present data on influenza subtypes detected by
15 several of these GEIS network partners.

16 I'll reiterate again that influenza
17 surveillance has been impacted significantly at these
18 sites. Restrictions and lockdowns resulting in reagent
19 shortages, shipping delays, and staffing reductions
20 have impaired normal surveillance activities in an
21 environment where many resources were being shipped to

1 COVID surveillance and where flu rates were already
2 diminished by the public health measures implemented in
3 response to the pandemic. Although surveillance
4 efforts for DoD on the next few slides were lower than
5 normal, influenza was detected in all the global
6 combatant commands for the first time since 2020. Some
7 notable regional examples include installation-wide
8 influenza A outbreaks in North America, frequent
9 detection of influenza A and B, including H1N1 in West
10 Africa, and persistent influenza in Nepal. So you'll
11 see this impact in the coming slides as I present our
12 data region-by-region.

13 On the following subtype circulation charts,
14 the MMWR week is along the X-axis, and the percentage
15 of positive samples is along the secondary Y-axis on
16 the right-hand side. The number of specimens submitted
17 is along the primary X-axis on the left-hand side.
18 Three years of data are shown starting with week 40 of
19 2019 on the left side of the X-axis to the most recent
20 data for 2022 on the right side. Different colors of
21 the bars indicate the different influenza types and

1 subtypes. This graph represents surveillance data for
2 military members, including recruits, and military
3 dependents residing within the United States, along
4 with select civilian populations near the U.S./Mexico
5 border.

6 Influenza A (H3N2) has been the dominant
7 subtype detected in North America after an extended
8 period with little to no influenza activity detected.
9 For the DoD, some of this activity has been localized
10 to specific areas of the United States, including
11 Maryland, Georgia, South Carolina, Illinois, and the
12 U.S./Mexico border, and has been outbreak-associated.
13 The data are well-aligned with data from the WHO and
14 provide more typing information for key DoD
15 populations.

16 Moving on to South America, the surveillance
17 data here comes from U.S. military and civilians as
18 well as local military and civilian populations within
19 Peru, Panama, Paraguay, Columbia, and Honduras. While
20 the WHO covers much larger regions, including temperate
21 South America, tropical South America, and Central

1 America and the Caribbean, the surveillance data from
2 DoD is consistent and shows that the most recent
3 influenza detected is primarily limited to influenza A
4 (H3N2). Looking now at Europe, this graph represents
5 surveillance data from military members and their
6 dependents residing in 10 countries in Europe. This
7 seasons influenza activity is still quite low. The few
8 positives that were detected have been influenza A
9 (H3N2) and influenza A un-subtyped. Much of the
10 sampling for this region was out of Italy, Germany, and
11 Georgia, which limits the generalizability of this
12 findings and likely explains the lower counts and
13 positivity compared to the WHO data in most recent
14 months.

15 Moving on to our surveillance in Asia. These
16 data represent U.S. military personnel and civilians as
17 well as select local national populations within a
18 large number of Asian countries. The DoD was able to
19 provide key data during the pandemic for a number of
20 countries compared to what we see with the WHO.
21 Moderate levels of influenza A H1N1 and H3N2 and

1 influenza B circulated in 2020 and 2021. There was
2 sustained influenza activity in Nepal for several
3 months, which was driving the DoD data shown here more
4 recently. The large number of influenza B detection
5 shown in late 2021/early 2022 confirms surveillance
6 activities where the DoD does not have a significant
7 infectious disease surveillance presence, such as
8 China, Sri Lanka, and India.

9 Now, looking over at the Middle East, this DoD
10 graph represents surveillance data from U.S. military
11 and civilians as well as select local national
12 populations within eight countries in the Middle East.
13 The majority of the data reflects sampling from Egypt
14 and Jordan for the most recent season, with relatively
15 little data from Afghanistan, Bahrain, and Kuwait.
16 Which may explain the discrepancies between the two
17 graphs. Influenza remained low in this population in
18 the region. There was some influenza A activity
19 detected, but otherwise, levels stayed low.

20 Moving on to East Africa. The DoD
21 surveillance in East Africa comes from foreign military

1 and civilian populations in Kenya, Tanzania, and
2 Uganda. Influenza activity was present throughout the
3 pandemic, and levels remain steady across the three
4 countries with periodic spikes in Kenya and Uganda.
5 Influenza A (H3N2) was the predominant type detected,
6 while influenza B was also circulating at low levels.
7 The DoD data is slightly inconsistent with what the WHO
8 data show here, although the number of countries
9 surveilled by the WHO is larger than DoD. WHO data
10 show low levels of influenza A (H1N1) circulating in
11 Tanzania, which is a region where DoD only reviews a
12 few samples per week.

13 Finally, looking at West Africa, the DoD
14 surveillance data presented here primarily comes from
15 foreign military and civilian populations in Ghana.
16 When compared with the surveillance data from the WHO
17 it's clear that they are consistent with respect to
18 types of influenza in circulation, and timing. The
19 data suggests that Ghana's a good surveillance proxy
20 for the region for DoD. Moving forward here, at the
21 Naval Medical Research Center, NMRC, some of the

1 current flu samples from USAFSAM were tested for
2 antigenic reactivity against reference Antisera shown.

3 The highest dilution of Antisera that showed
4 50 percent neutralization against each sample by HINT
5 assays is shown. All samples showed high reactivity to
6 Antisera against A/Darwin/9/2021 and A/Darwin/6/2021,
7 the Southern Hemisphere 2022 (H3N2) vaccine strain.
8 Data from the previous slide was analyzed by a
9 cartography program to generate the antigenicity map
10 shown here. All but one sample clustered together and
11 are antigenically similar to A/Darwin/2021, cell- and
12 egg-based. Sample 12, the purple drifts from the
13 cluster. We will also see this is the phylogenetic
14 tree that's presented later.

15 And this slide shows the metadata from the
16 samples, illustrating two different subgroups, D53G and
17 D53N. The three substitutions in the sample number 12,
18 S156H, S205F, and A212T appear to have an impact on
19 antigenic reactivity. So, in summary, our influenza
20 surveillance data from our global lab partners is still
21 limited for this flu season. North America influenza A

1 (H3N2) has been the dominant type. In South America
2 positivity for H3N2 has increased in recent months.
3 Europe has seen low levels of influenza. Asia has had
4 moderate activity lately with H3N2 and influenza B. In
5 the Middle East we've seen low levels of primarily
6 influenza A detected. In East Africa moderate
7 influenza has been noted with all subtypes detected.
8 And West Africa is one of the only regions with H1N1
9 circulating.

10 Moving on now I will discuss the phylogenetic
11 analysis completed this year by the U.S. Air Force
12 School of Aerospace Medicine, or USAFSAM. Looking at
13 the geographical distribution, sequences from 450 total
14 influenza positive specimens were collected with one
15 A(H1N1)pdm09 from the United States, one B/Yamagata
16 from the United Kingdom, and 448 A(H3N2) collected from
17 Germany, Italy, Peru, the United Kingdom, and the
18 United States. Specimens were collected as part of the
19 DoD Global Respiratory Pathogens Surveillance Program
20 at USAFSAM in addition to specimens contributed by
21 Eglin Air Force Base, Landstuhl Regional Medical

1 Center, and specimens and sequence provided by the
2 Naval Health Research Center in San Diego, and the
3 Naval Medical Research Unit 6 in Peru.

4 All 448 of the A(H3N2) hemagglutinin sequences
5 collected were in clade 3C.2a1b.2a2 with 405 sharing
6 the substitution D53G/D104G/L157I/S262N and K276R. And
7 27 shared D53N/D96S/I192F, and N378S. Four viruses
8 shared S205F and A212T, which are circled in yellow on
9 the tree. One of these viruses was antigenically
10 characterized and showed antigenic distinction from
11 reference virus strains and the other surveillance
12 strains sharing either D53G or D53N. The 2021 Northern
13 Hemisphere vaccine strain is marked by an orange star.

14 The 2021/2022 Northern Hemisphere vaccine
15 strain is marked by a red star, and the 2022 Southern
16 Hemisphere vaccine strain, a 3C281B.2a2 virus, is
17 marked by a pink star. N96S causes the addition of a
18 glycosylation motif and two individual losses of
19 glycosylation motifs occurred. A/Maryland/02/2021 a
20 clade 3C2a1b.2a2 reference virus, sharing the D53
21 substitution group, was most closely related to the

1 circulating strains observed. Circulating A(H3N2)
2 clades over the last three years are shown here.
3 Illustrating much higher genetic diversity. The
4 2018/2019 and 2019/2020 season. Extremely low
5 circulation and diversity in the 2021 season, and an
6 increase in circulation for the 2021/2022 season.
7 Although all the strains in 2021/2022 season fall under
8 clade 3C2a1b.2a2, an increase in diversity from last
9 season is also observed when considering the emerging
10 subgroups. Distribution of the previous two vaccine
11 strain selections are shown in the text boxes color
12 coordinated with the associated clade of each strain.

13 Neuraminidase sequences were available for 428
14 of the influenza positive specimens. The NA
15 phylogenetic tree is very similar to the HA
16 phylogenetic tree, indicating a similar genetic
17 trajectory and relation of circulating strain NAG to
18 vaccine and reference strain NA. The substitution
19 S329N caused the addition of a glycosylation motif and
20 a minor branch location in the tree, which corresponds
21 to virus and sharing the D53N HA substitution group.

1 A/Maryland/02/2021 once again falls well within the
2 majority of the strains represented.

3 So, to sum up, the one influenza A(H1N1)pdm09
4 specimen sequence was in clade 6B.1A-5A.1 and contains
5 the substitutions R113K and H399N, which are shared
6 with the 5A.1 reference strain. The reference strain
7 A/Pennsylvania/02/2021, the one influenza B specimen
8 available for characterization was a Yamagata lineage
9 virus in the say clade Y3 that has been circulating for
10 many years and is well-covered by B/Phuket/3073/2013.
11 All influenza A(H3N2) specimens were in clade
12 3C.2a1b.2a2 with 94 percent sharing the substitution
13 D53G/D104G/L157I/S262N and K276R.

14 Now I'd like to review the vaccine
15 effectiveness estimates performed by our Armed Forces
16 Health Surveillance Division Epidemiology and Analysis
17 Branch. To start off I'll first mention what typically
18 comprises our annual vaccine effectiveness analysis.
19 We usually have three partners that contribute to this
20 effort, the Armed Forces Health Surveillance Division
21 satellite at USAFSAM usually provides vaccine

1 effectiveness analysis for our active duty
2 beneficiaries within the Department of Defense and the
3 Naval Health Research Center provides data for vaccine
4 effectiveness in military basic training. However, the
5 small number of positive results available for those
6 partners prevented any kind of meaningful analysis of
7 vaccine effectiveness in this population, so I will not
8 be presenting those results today.

9 The Armed Forces Health Surveillance Division
10 Epidemiology and Analysis branch conducts our vaccine
11 effectiveness analysis for active duty personnel.
12 Unfortunately, we do have some data to present for that
13 population, which I will discuss on the next few
14 slides. The study design for this analysis is
15 case/test negative control design on active component
16 personnel from all the military services, including
17 those stationed within the continental United States,
18 or CONUS, and those stationed in foreign locations,
19 OCONUS, during the September 1, 2021, to February 12,
20 2022, time period.

21 These cases were lab-confirmed by either

1 positive rapid test, RT-PCR, or culture assays. Test
2 negative controls were those that presented for care,
3 tested negative for the flu by either RT-PCR or culture
4 assay. Those that were negative by rapid tests alone
5 were excluded from the analysis. Models were adjusted
6 for sex, age, category, prior vaccination, and month of
7 diagnosis. I'll present both accrued vaccine
8 effectiveness for both influenza A and influenza B in
9 the next slide. Inactive influenza vaccine was the
10 only vaccine type used in these study subjects. It's
11 also important to note that our active duty population
12 is a highly vaccinated population, as the flu vaccine
13 is compulsory for active duty personnel. So 85 percent
14 of the study subjects had been vaccinated for flu
15 within the previous five years.

16 We had 1,303 influenza A and 165 influenza B
17 cases to include in the analysis. The higher
18 proportion of cases were identified in December, 55
19 percent, with test negatives spread out over the entire
20 study period. Our breakdown by age group of both cases
21 and controls is shown here. U.S. military population

1 is relatively young compared to the general U.S.
2 population, which will limit the ability to generalize
3 these results to the broader U.S. population. Here are
4 the results of the analysis showing overall vaccine
5 effectiveness and then for both influenza A and B. So,
6 in summary, the overall mid-season vaccine
7 effectiveness was 36 percent, but do remember that this
8 is the relatively young, active duty military
9 population only. It was somewhat higher for influenza
10 B at 59 percent, indicating moderate protection and
11 then notably lower at 33 percent for influenza A.

12 Here are notes on vaccine strain
13 recommendations. The A(H1N1)pdm09 strain
14 recommendations inhibit 6B1A5A.2 viruses well and
15 6B1A5A.1 viruses less well, however, we feel that our
16 one 6B1A5B.1 virus from Europe is not representative
17 enough to agree or disagree with this recommendation.
18 The A(H3N2) strain recommendations inhibit 3C2A1B.2a2
19 well, as also suggested by our antigenic data on the
20 overwhelming majority of our viruses. The slight
21 antigenic distinction of a virus with the substitution

1 S205F and A212T representing a small number of viruses
2 from Europe will likely have little impact. We do not
3 have any B/Victoria sequence data for the 2021-2022
4 season and therefore cannot comment on that strain
5 selection. The B/Yamagata strain recommendation
6 inhibits Y3 virus as well, however, we feel that our
7 one B/Yamagata sequence is not representative enough to
8 agree or disagree with that recommendation.

9 I'd like to acknowledge our colleagues at the
10 Armed Forces Health Surveillance Division as well as
11 our partner labs, we are incredible grateful for your
12 contributions to this presentation and in completing
13 all of our surveillance efforts. And we have a second
14 slide because we have a lot of great colleagues. And
15 that concludes my presentation, so I'm open for
16 questions.

17 Q AND A SESSION

18
19 **DR. HANA EL SAHLY:** Thank you, Dr. Courtney,
20 for this presentation. Michael is going to put me back
21 as presenter, and here we go. I have two committee

1 members with questions, beginning with Dr. Shane. Dr.
2 Shane?

3 **DR. ANDREA SHANE:** Yes, thank you so much, and
4 thank you for that very helpful and informative
5 presentation. I just had a question, you mentioned
6 that the surveillance included dependents of the armed
7 forces members. I was wondering if you have any data
8 on that specifically, with focus mostly with respect to
9 vaccine effectiveness or if you don't have that
10 information? Thank you.

11 **DR. COURTNEY GUSTIN:** Sure. Normally that is
12 part of the presentation, but this year those partners
13 had reported that they didn't have enough data to do a
14 meaningful analysis of vaccine effectiveness in the
15 dependent-only population.

16 **DR. ANDREA SHANE:** Thank you.

17 **DR. HANA EL SAHLY:** Dr. Courtney, is there any
18 severe disease or hospitalization cohorts, or is it
19 mostly out-patient mild disease?

20 **DR. COURTNEY GUSTIN:** I don't have that data
21 close at hand, I'd have to follow-up with that, and I

1 can get back to you later today on that.

2 **DR. HANA EL SAHLY:** Second in line, Dr. Offit.
3 Dr. Offit?

4 **DR. PAUL OFFIT:** Yes, thank you for that clear
5 presentation. Hana, you just asked my question, I just
6 wanted to know what we had knew about vaccine
7 effectiveness from mild, moderate or severe disease,
8 which is really data we need to get, so hopefully we'll
9 get those data soon. Thank you. Thank you, Courtney.

10 **DR. COURTNEY GUSTIN:** Sure, I'll follow-up
11 with our partners and see if I can, I'll get it to the
12 hosts of the conference today as soon as I can.

13 **DR. HANA EL SAHLY:** Thank you. I do not see
14 any raised hands, so I want to thank Dr. Courtney for
15 taking the time and presenting this data to the
16 committee. Our next presenter is Dr. Manju Joshi
17 (audio skip) in Quality and Office of Compliance and
18 Biologics Quality at CBER. Dr. Manju Joshi is going to
19 go over the candidate strains and potency reagents.

20

1 **CANDIDATE VACCINE STRAINS AND POTENCY REAGENTS**

2

3 **DR. MANJU JOSHI:** Thank you, Dr. El Sahly. My
4 name is Manju Joshi, and I am from the Division of
5 Biological Standards and Quality Control in Office of
6 Compliance and Biologics Quality at CBER, FDA. In
7 today's presentation I'm going to be covering the WHO
8 recommendations for 2022-23 Northern Hemisphere
9 influenza vaccine. I'll give you an update on the
10 situation with the availability of potency reagents for
11 each of the recommended strains. I'll give a little
12 bit of comments about how we're planning for the
13 dispensing of vaccines for 2022-23 season. And, since
14 this is my chance to address, and I know there are a
15 lot of vaccine manufacturers that are also listening
16 in, they're on this meeting, I'll just put some general
17 remarks which will be not so much for the committee
18 members, but to the general audience and in particular
19 the vaccine manufacturers.

20 So, for influenza A of H1N1 type, the WHO
21 recommended viruses for 2022-23 Northern Hemisphere

1 season vaccine is same as it was for 2021 Northern
2 Hemisphere season and also the same virus was
3 recommended for 2022 Southern Hemisphere season. The
4 recommendation is being for egg-based vaccines
5 A/Victoria/2570/2019 H1N1pdm09-like virus. But for
6 cell culture- or recombinant-based vaccines the WHO
7 recommendation is the A/Wisconsin/588/2019 pdm09-like
8 virus. In the interest of the time, I haven't listed
9 all the candidate vaccine viruses, they are available
10 for each of the groups. But I have provided the
11 information so that anybody interested can look up all
12 the different viruses available with the WHO site.

13 And, so, here I'm going to give you an update
14 on the status of the various potency reagents who are
15 testing of A(H1N1)pdm09-like component of 2023 vaccine.
16 Let me make it clear, this is based on if the committee
17 approves the recommendation which provided by WHO, we
18 have the reagents available for testing of vaccines.
19 There have been several viruses and reassortants made
20 available and at CBER, since we do have, for the
21 (inaudible) vaccine, we had prepared the reference

1 antigen and antiserum for A/Victoria/2570/2019 IVR-215
2 reassortant and those reagents are available from CBER.
3 Available from our collaboration partners, which are
4 from TGA and NIBSC had also prepared these reagents and
5 they are available from them as well.

6 Similarly, from any manufacturers who are
7 interested in using different reassortant from the same
8 group or A/Victoria/1/2020, our partners at NIID have
9 made these reagents available.

10 As far as H1N1 components for the cell
11 platform is concerned, CBER had prepared the reagents
12 for A/Delaware/55/2019, which was one of the
13 recommended virus. And those both reference antigen
14 and antiserum are available.

15 Last year, cell platform people had decided to
16 use another virus from H1N1 component, which is
17 A/Washington/19/2020 virus from the same group. We did
18 make a reference antigen standard and made it available
19 for use. Similarly, for the recombinant platform, they
20 had chosen to use A/Wisconsin/588/2019 from this group
21 and CBER has made the reagents available for them as

1 well.

2 So, this is just to give you an idea that if
3 this strain is selected by committee, that the reagents
4 for each of these are available. Coming to the
5 influenza A of H2N2 type. WHO recommended virus for
6 2022 Northern Hemisphere season vaccine is different
7 from that which was recommended last year for 2021-22
8 Northern Hemisphere season. But it is same for 2022
9 Southern Hemisphere season.

10 So the recommendation for egg-based vaccine is
11 A/Darwin/9/2021(H3N2)-like virus, and that for cell
12 culture- and recombinant-based vaccine it is
13 A/Darwin/6/2021-like virus. Again, the candidate
14 vaccine virus list is available at the WHO website,
15 shown here on my slide.

16 If Committee were to approve this strain for
17 inclusion for the US vaccine, the status of the
18 reagents is as follows. This strain was recommended
19 for Southern Hemisphere campaign. We, at CBER as well
20 as (inaudible) have worked to produce reagents for
21 Southern Hemisphere campaign and exclusive strains

1 continuous reagents will be made available. At CBER,
2 we had prepared reference antigen reagents and PCR for
3 A/Darwin/9/2021, for a cell (inaudible) reassortant.
4 And those, out of the interest of time, again, I'm not
5 reading all the lot numbers or anything, but the
6 reagents as shown on the table are available.

7 Our partners, NIBSC has also prepared the
8 similar reagents for -- NIBSC went ahead and prepared
9 reagents for A/Darwin/9 IVR-228 reassortant if anybody
10 had to use. And, similarly, reagents for A/Darwin/6
11 IVR-227 reassortant for all egg platform are the three
12 so far I have said but made available by other
13 partners. We here at CBER prepared reference antigen
14 reagents and calibrated it for A/Darwin/11/2021 for the
15 cell platform aspect.

16 And I just wanted to point out that we were
17 closely partnered with other collaborators, so that's
18 why this reagent planning is done at a group just to
19 make sure as many reagents can be prepared and there is
20 more choice of reagents for the different strains are
21 selected.

1 Coming to the influenza B from B/Victoria
2 lineage. WHO recommended virus for the upcoming season
3 for trivalent and quadrivalent vaccines, different from
4 what was recommended for '21-'22 Northern Hemisphere
5 season. Yet, again, it is same as 2022 Southern
6 Hemisphere season.

7 Then, WHO recommended that for egg-based
8 vaccines, B/Austria/1359417/2021 from B/Victoria
9 lineage, be the candidate virus. And for cell culture
10 and recombinant was the similar virus recommended. If
11 this was to be included in the vaccine, again, the
12 status of the reagents for vaccine testing are listed
13 here in the table.

14 Since this was recommended for Southern
15 Hemisphere campaign we had worked to prepare the
16 reagents. Here at CBER we work to prepare reference
17 antigen reagents and antiserum for B/Michigan/01/2021
18 for egg platform. And those antigens Lots are
19 available and even antiserum are available. Similarly,
20 our partners TGA and NIBSC have prepared the reagents
21 for B/Austria reassortant BVR-26 and those are

1 available from them as well.

2 Again, in our domain, we have worked to
3 prepare a cell reagent for B/Singapore/WUH4618/2021
4 strain, and the reference antigens are 2115 is
5 available along with the antiserum for testing of this
6 component in cell-based vaccine, if it's selected.

7 Coming to the influenza B, which I call the
8 second B-strain, which is always from the B/Yamagata
9 lineage, the WHO has recommended that virus for '22-'23
10 Northern Hemisphere season quadrivalent vaccine is the
11 same as what was last year. It was the same in 2022
12 Southern Hemisphere season and as all the previous
13 presentations have pointed out, that this strain has
14 been going on seems like forever.

15 So, for egg-based vaccine, the WHO
16 recommendation for the quadrivalent, the second B-
17 strain would be B/Phuket/3073/2013 from Yamagata
18 lineage for both -- this is the same for cell culture
19 and recombinant vaccines as well. And you can check
20 the list of all the candidate vaccine viruses from this
21 group at the WHO website.

1 Taking a quick look at what is the situation
2 of the reagents that are available for testing of this
3 component of the vaccine. So, CBER has the reagent
4 available for B/Phuket for egg-based vaccine, both
5 antigen and antiserum are available, even the reagents.
6 Since this strain has been going for so long, the
7 others ERLs, NIBSC, TGA, and NIID have reagents
8 available as well with them.

9 For the reassortant BVR-1B for the B/Phuket
10 strain, TGA has prepared reagents and they have been
11 made available. We at CBER have worked and prepared
12 the reagents for the B/Singapore/INFTT-16-0610/2016
13 which is for the cell platform. And represented in an
14 antiserum for testing this component is cell-based
15 vaccine is available.

16 In addition in that, the manufacturers of cell
17 platform had chosen to use B/Utah strain from the same
18 group and CBER has provided those reagents as well. We
19 have even prepared a reagent for the B/Phuket for
20 recombinant platform, and those reagents are also
21 available from CBER. So, if committee approves this

1 strain, again, the reagents are in place.

2 Now question comes how are we ready for
3 preparing and calibrating of any new reagents needed?
4 As I pointed out, since the strain recommendation for
5 the B/Victoria reagent as seen are the same as Southern
6 Hemisphere campaign, we have prepared reagents for
7 those two for egg and cell platform. So now we are
8 ready to work with ERLs and the manufacturers to
9 prepare and calibrate the reagents required for potency
10 testing of A/Darwin-like component in recombinant
11 vaccine as well as for B/Austria-like component
12 recombinant vaccine if these recommendations are
13 finalized and the recombinant vaccine manufacturers
14 will acquire these reagents.

15 In addition, we in the DBSQC at CBER are ready
16 to calibrate any reagents, any new reagent, if a
17 manufacturer chose to pick up a new reassortant or new
18 strain for their manufacturing company. So we are
19 ready to take on that and proceed with it.

20 Coming down to -- I think this is not interest
21 to the committee as such, but I'm just putting it out

1 mainly for our manufacturers who are listening on this
2 call. And we would like the manufacturers to provide
3 us the following information as I have shown here,
4 which includes the strain name, reassortant or vaccine
5 virus they are planning to use in manufacturing. Since
6 there are several reagents available, which reagent
7 referencing antigen and antiserum and their supplier
8 they're trying to acquire.

9 I have considered that having this information
10 is extremely important for us to plan our laboratory
11 activities. All of us were planning the work around
12 reagent calibration. Depending on what reagents are
13 getting used, we have to think about importing reagents
14 from other ERLs if they are the one manufacturer
15 chooses to use. And there's a big bulk of activities
16 which involve the testing of (inaudible) which they
17 call monovalent bulk testing and eventually, the Lot
18 release testing. So, for a smooth operation of the
19 whole process of vaccine testing, we would like
20 manufacturers to send us this information so that it
21 helps us in planning.

1 Continuing with some more comments. I want to
2 let manufactures know that only CBER-authorized
3 reagents should be used to test potency of vaccines
4 marketed in US. So that's the reason why it would be
5 very helpful if you just consulted us, let us know what
6 your plans are, and then we can move forward with it.

7 When it comes to submitting the samples for
8 monovalent samples, they should be submitted to
9 Division of Biological Standards and Quality Control.
10 Please email me, my email address is here, regarding
11 dispatch of sample and test results. And always cc on
12 the email my lab chief, Dr. Shahabuddin, his email is
13 included here as well.

14 And if manufacturers have any inquiries
15 regarding CBER Reference Standards and Reagents about
16 availability, shipping, please contact CBER Standards
17 at the email address provided here.

18 And, one last thing I would like to add is,
19 please send us -- manufacturers, we would appreciate it
20 if you can send your feedback, comments on the
21 availability, suitability and useability of reagents we

1 are providing and any other aspect of our services to
2 our Influenza Mailbox, the address is
3 CBERinfluenzafeedback@fda.hhs.gov. We monitor that
4 mailbox and if there are any questions or any
5 communication is needed we can do that as well. So,
6 thank you, and I can take any questions.

7

8

Q AND A SESSION

9

10 **DR. HANA EL SAHLY:** Thank you. Dr. Joshi. Are
11 there any questions for Dr. Joshi? I see none, but I
12 want to thank you for all the hard work getting the
13 laboratory references and potency reagents ready for
14 this big task.

15 **DR. MANJU JOSHI:** Thank you.

16 **DR. HANA EL SAHLY:** As a follow-up to the
17 presentation by Dr. Groshkopf this morning, Dr.
18 Groshkopf would like to provide additional comments.
19 Dr. Groshkopf? Dr. Groshkopf, please unmute yourself
20 and turn your camera on.

21 **DR. LISA GROSHKOPF:** Okay, I'm sorry. I

1 think I'm unmuted now, yes?

2 **DR. HANA EL SAHLY:** You are.

3 **DR. LISA GROSHKOPF:** Okay, thank you. In
4 checking with my surveillance colleagues regarding the
5 question concerning surveillance of coinfections, I'm
6 told that in FluSurv-NET and COVID-NET they do look for
7 patients with hospitalizations reported in both
8 systems. And they also look through virologic
9 surveillance data from public health labs to pull
10 specimens that got tested for both flu and Sars-CoV-2.
11 So there is some following of such coinfections within
12 those systems.

13 **DR. HANA EL SAHLY:** Great. So I guess this
14 data will be forthcoming in application or MMWR later
15 maybe?

16 **DR. LISA GROSHKOPF:** I (audio skip).

17

18 **COMMENTS FROM MANUFACTURER REPRESENTATIVE**

19

20 **DR. HANA EL SAHLY:** Thank you for the follow-
21 up. Next is Dr. Beverly Taylor. Dr. Beverly Taylor is

1 head of Influenza Scientific Affairs, WHO and IFPMA
2 Lead Seqirus, a CSL Company. Dr. Taylor will provide
3 the influenza vaccine manufacturer's perspective.

4 **MR. MICHAEL KAWCZYNSKI:** Hold on, Dr. Taylor,
5 there we go.

6 **DR. BEVERLY TAYLOR:** Hi, can you hear me okay?

7 **MR. MICHAEL KAWCZYNSKI:** Yes, we can.

8 **DR. BEVERLY TAYLOR:** Okay. Thank you very
9 much. My name is Dr. Beverly Taylor, I work for
10 Seqirus Vaccine, but I am giving this presentation on
11 behalf of influenza vaccine manufacturers. Just for
12 your information, IFPMA is International Federation of
13 Pharmaceutical Manufacturers and Associations. And
14 it's the international industry association based in
15 Geneva.

16 I'd like to thank the VRBPAC committee for
17 giving me the opportunity to provide the industry
18 perspective today. And I'd like to point out that this
19 summary was prepared from a variety of public sources,
20 and it has been reviewed by Seqirus, GSK, Sanofi, and
21 AstraZeneca. Okay, and my disclosure statement is I am

1 an employee of Seqirus, and I do own shares in the
2 company.

3 So the key messages in the presentation today
4 are the key components of a successful vaccination
5 campaign, or vaccine manufacturing campaign. Having a
6 look at the influenza surveillance during the COVID-19
7 pandemic, we've seen some of that today, but just
8 reinforcing that. The strain changes that we had for
9 the Northern Hemisphere '21-'22 season and the reagents
10 supply for those strains. An overview of the
11 manufacturing campaign timelines. The continued
12 challenges that we see due to the COVID-19 pandemic. I
13 also want to give an update on the Nagoya Protocol.

14 So what do we need for a successful influenza
15 vaccination campaign? So, obviously, we want to have
16 the vaccine as well-matched as possible to the
17 circulating influenza strains. And that's why it's so
18 important for us to have the ongoing and robust
19 surveillance that provides WHO with that, and VRBPAC
20 with that information. We also need the timely
21 availability to vaccinate before the upcoming influenza

1 season, so that means that we, as manufacturers, have
2 to have our vaccines ready in plenty of time for that
3 to be achieved.

4 And that, in turn, means that we need the
5 supply of the candidate vaccine viruses and the potency
6 assay reagents in good time. We also need sufficient
7 vaccine doses to support the recommendations in
8 increasing immunization rates, and for this we need to
9 be able to evaluate the candidate vaccine viruses and
10 work out which viruses work best in our manufacturing
11 platforms. And that we have some time to optimize the
12 yields. And all these factors feed into the influenza
13 vaccine strain selection, and that strain selection
14 impacts the timing of our supply. I know we've seen a
15 lot of surveillance slides and we can see that the
16 impact that the COVID-19 pandemic had on flu
17 circulation, but I think it's just worth looking. I
18 took the same week in 2020 and 2021, so week five of
19 2020, we had 25, in the U.S., approximately 25,000
20 positive samples for influenza. Compare that in 2021
21 week five and we have less than a hundred. So that

1 just shows you the impact of the measures that we took
2 to control COVID and the COVID pandemic had had.

3 However, it's important to say that there were
4 still pockets, as was discussed before by committee, in
5 Southeast Asia and Africa, and there were antigenically
6 distinct viruses detected. So there was still a need
7 to obtain the composition of the vaccine even though
8 flu circulation levels were so low. And we did
9 continue to see the viruses evolving, so there are just
10 the next strain graphs that have been shown by Dr.
11 Wentworth previously. And you can see the activity of
12 the viruses is continuing, except with the Yamagata
13 virus, as Dr. Wentworth indicated, we have not seen any
14 viruses. Although I was very interested to hear in the
15 previous presentation that there was one B/Yamagata
16 detected, I think it was in Europe. But, from the WHO
17 surveillance, no B/Yamagata viruses have been confirmed
18 since 2020.

19 So, in the last year, the VRBPAC committee
20 recommended the formulation for the seasonal vaccine,
21 and there were two changes. So we have a change to the

1 H1N1 to the A/Victoria/2570/2019 and to the A/Cambodia,
2 I'm not going to say that number, 2020, that was for
3 the egg-based. And cell- or recombinant-based we had
4 recommendations for A/Wisconsin/588/2019 or the
5 A/Cambodia for the H3N2. An also, for the trivalent
6 influenza vaccine, the committee recommended that the
7 B/Victoria lineage virus be used and obviously there
8 were two strain changes from the previous season.

9 Regarding the supply of the potency reagents
10 for this Northern Hemisphere season. CBER again
11 confirmed that they would accept TGA and NIBSC reagents
12 for testing of egg-based vaccines, provided that we, as
13 manufacturers, supplied them with that information at
14 the beginning of the season, and specified which
15 reagents that we were going to use. The timing of the
16 calibration dates are given here, there were a number
17 of the calibrations of the reagents were done, the
18 calibrations were done for the Southern Hemisphere, and
19 so they were available late 2021. And then, for the
20 A/Wisconsin recombinants, the calibration date was the
21 end of May.

1 And if we look at the supply of the H3N2
2 potency reagents, we can see that for all of the
3 candidate vaccine viruses that were being used by
4 manufacturers, whether that be egg, cell, or
5 recombinant, the calibration dates for the reagents
6 were in late May or in June. Which really is within
7 the normal timeframe that we would expect the
8 calibrations. I just want to say thank you to CBER and
9 the other ERLs because despite the ongoing concerns
10 about reduced number of flights, issues with
11 international couriers, the ERLs prioritized the
12 calibration of reagents and the timing of the
13 calibration values. Which are essential for us to be
14 able to formulate and release our final vaccines, was
15 similar to previous years. And I just want to thank
16 Dr. Joshi for the presentation that she just gave and
17 the information that she provided to the manufacturers.
18 And we are prepared to supply the information that she
19 outlined in the normal format that we do. So thank you
20 very much for that, Dr. Joshi.

21 So we made the point before that it takes

1 teamwork to get influenza vaccines across the finish
2 line. And we have used before a relay race analogy.
3 And we say that the first runner is at full speed, and
4 this is the WHO collaborating centers, the ERLs, the
5 reassortant labs are going at full speed to supply us
6 with the candidate viruses. And then the receiving
7 runner starts running before the handoff. So we, as
8 manufacturers, are starting to produce at-risk before
9 the candidate vaccine virus or the virus selection has
10 been made, so that we are maximizing our chances to
11 supply within the expected timeframes. And then we see
12 the runner is at full speed at handoff.

13 And, so, we've already started manufacturing
14 at-risk and we're also preparing receiving the
15 candidate vaccine viruses and we're ready to use the
16 new strains and get ready for formulation. And
17 throughout the race there needs to be strong planning
18 and good communication. And we do have bi-weekly WHO
19 industry teleconferences. We also have now in place a
20 cross-functional working group influenza hub, which is
21 hosted by NIBSC in the U.K., and that means that we can

1 get real-time information on candidate vaccine viruses
2 and where reagent preparation is up to. Rather than
3 just waiting for the bi-weekly meetings. So that has
4 been incredibly helpful in our planning.

5 We also have additional challenges for
6 influenza. We don't only have one baton being passed,
7 we have multiple batons, we have candidate vaccine
8 viruses, we have reagents, we have different vaccine
9 types. And there are also multiple providers, so we
10 work with the WHO collaborating centers, the essential
11 regulatory labs, the reassortant labs, and all these
12 pieces have to come together in order for us to have a
13 successful campaign. So we always have hurdles during
14 the manufacturing campaign, and the hurdles in the
15 Northern Hemisphere 2021-'22 campaign were two strain
16 changes. I mean, this is not unusual, it's part of
17 working with influenza, we expect this. Every time
18 there is a strain change, there is lots of work to do.
19 We have to qualify the new candidate viruses, we have
20 to make annual submissions to update the viruses. So
21 strain changes do add to the workload.

1 We've also seen Nagoya Protocol issues, which
2 I'll discuss in a bit more detail in later slides. We
3 had challenges with materials and component supplies
4 this year. And that's because, for good reasons, a
5 number of materials and components were redirected
6 towards vaccines for COVID-19. However, we have to
7 understand that the influenza virus was still very
8 important and that we still needed to have the
9 materials and components that we needed to deliver the
10 flu vaccine on time. And then with the ongoing impact
11 of the COVID-19 pandemic on transport and freight.

12 So, you've seen this slide before, but this is
13 our, the annual influenza vaccine manufacturing
14 timeline for U.S. supply. So you can see, if we start
15 at the left-hand side of the graphic here, you can see
16 an orange box where we start production at-risk. So we
17 will start, prior to the strain recommendation, as
18 early as January. So we have a couple of months before
19 the VRBPAC recommendation where production starts at-
20 risk. And, this again, is where the surveillance and
21 the information sharing is really important because in

1 order that we don't lose the benefits of starting
2 production early and at-risk, we need to choose a
3 strain that is least likely to change in the
4 recommendation. So that's why we're constantly
5 monitoring the surveillance and trying to get as much
6 transparency with the information as possible.

7 Once the strain selection's been made, we then
8 go on to produce the other strains. Each strain is
9 manufactured separately and then, when we have
10 manufactured material from each of the strains, we can
11 then, and the reagents are available, we can then
12 formulate the final vaccine and then obviously fill and
13 package. So, a Northern Hemisphere campaign, about 500
14 million doses are produced and distributed globally.
15 It takes about six months to get to the first dose
16 currently, and eight months to the last dose. So it's
17 a very tight window and any delay or any reason why we
18 can't move forward will impact our ability to start in
19 time.

20 So, Dr. Wentworth mentioned the one year that
21 we had a delay of a month for an H3N2 recommendation,

1 that certainly put pressure on this timeline. We could
2 still produce some of the other strains, not at-risk,
3 but we could still go ahead and produce the other
4 strains, but until we had the H3N2 strain produced we
5 weren't, and the reagents, we weren't able to formulate
6 the vaccine. So understanding why the delay was
7 needed, but it definitely does have an impact and put
8 pressure on the system. And the other thing I want to
9 highlight from this is it's really important for
10 manufacturers to get early demand planning. So we need
11 to plan how much we're going to make for the campaign
12 and at what point we need to start the production at-
13 risk if we're to ensure sufficient supply of the
14 vaccines for the season.

15 This graph is just showing the U.S. influenza
16 vaccine distribution and we have this current season as
17 well as the previous two seasons. The purple, the
18 light purple line is showing the vaccine distribution
19 for the 2019-2020 season. The green line at the top is
20 showing the 2021-'22 season, sorry, no, that's the
21 season before, 2020-'21. And then the blue line, which

1 is difficult to see because in the later weeks it falls
2 under the 2019-2020 line, that is actually this current
3 Northern Hemisphere. And I think we're up to about 174
4 million doses distributed for this season. So we
5 responded, as manufacturers, in the Northern Hemisphere
6 2020-'21 season with, it was actually about an 11
7 percent increase in the number of doses versus the
8 previous season. And that was because of the increase
9 in demand, because of the COVID pandemic, and people
10 were afraid of the twin-demic, and so, demand went up
11 and manufacturers were able to respond to that.

12 Demand for this Northern Hemisphere season was
13 lower, but it was similar to the Northern Hemisphere
14 2019-'20 season. However, we have seen the flu
15 vaccination rates have been slower this year and were,
16 at least initially, lower overall than the previous two
17 seasons. So the graphic in the top right-hand corner
18 is just showing it's got years on the X-axis and
19 millions of doses on the Y-axis. And you can just see
20 that over the years the total vaccines distributed has
21 gone up, but it's all got to fit into that tight, tight

1 timeframe for that manufacturing window that we have.
2 So, even though the number of doses have gone up so
3 significantly, we've still been able to deliver the
4 vaccines within that window.

5 So we're continuing to see challenges due to
6 the COVID-19 pandemic this Northern Hemisphere season
7 or leading up to the selection of the viruses for this
8 season. Despite increased testing by the National
9 Influenza Centers, we saw only low levels of influenza
10 detected. There were pockets of activity, as has been
11 said, in Southeast Asia, in parts of Africa and China.
12 But it wasn't clear that as things opened up that the
13 viruses that were isolated in those pockets would be
14 the viruses that would circulate more widely. So it
15 made this decision very difficult. Different viruses
16 were isolated in different regions, so, again, it was
17 difficult to predict which one of those viruses would
18 predominate for the Northern Hemisphere '21-'22 season.
19 There were also a long number of available virus
20 isolates for this season. And, again, for the Southern
21 Hemisphere 2022 manufacturing campaign, which means we

1 have less viruses, candidate viruses, to select from
2 and so, we have less choice in which ones we use on our
3 manufacturing platforms and so we might end up with
4 something that's less than ideal because we are not
5 able to pick the best one for our particular platform.

6 Again, it's been said before, we saw no
7 genetic sequence data or physical samples received for
8 B/Yamagata viruses, and that's almost two years now.
9 And, also, we continue to have a lack of clarity on
10 Nagoya Protocol and access and benefits sharing status
11 with a limited number of available viruses and some of
12 those viruses coming from countries that have Nagoya
13 Protocol legislation or national ABS legislation in
14 place that puts more uncertainty around our ability to
15 use those viruses in manufacturing.

16 I mentioned the supply chain challenges and
17 material shortages due to the prioritization of
18 materials for COVID-19 vaccines. And then, obviously,
19 we're concerned about slower and reduced influenza
20 vaccine uptake rates. I've just got a few slides on
21 Nagoya Protocol. I realize that many people on the

1 call won't be as familiar with Nagoya Protocol or
2 Access and Benefit Sharing legislation, so just a
3 little bit of background. So the Nagoya Protocol on
4 Access and Benefit Sharing is an international treaty
5 which is supplementary to the Convention on Biological
6 Diversity.

7 And it was adopted in 2010, and the objective
8 is fair and equitable sharing of benefits arising from
9 the utilization of genetic resources from a particular
10 country and, therefore, contributing to the
11 conservation and sustainable use of biodiversity. So
12 the Nagoya Protocol came forth in October 2014, and
13 that was after the 50th country ratified the protocol.
14 The U.S. is not a signatory or party to the Nagoya
15 Protocol, but that doesn't mean to say that entities
16 and, including manufacturers, that operate from the
17 U.S. could not be impacted by this legislation. So,
18 under the terms of the Nagoya Protocol, genetic
19 resources can be accessed subject to prior informed
20 consent from the country of origin once mutually agreed
21 terms have been reached.

1 And it's the responsibility of each party to
2 decide how they address pathogens. So whether
3 pathogens are included in that legislation or not. In
4 many cases, pathogens have been included. And, to
5 date, 134 countries have become party to the Nagoya
6 Protocol, and many have implemented the ABS
7 legislation, which could potentially impact pathogen
8 sharing. And not only the physical samples, but also
9 the use of digital sequence information or genetic
10 sequence data from those pathogens. So, obviously,
11 this impacts influenza. And the legislation differs in
12 each country, which poses challenges when you're trying
13 to interpret the requirements from that country. And
14 the other point that is important to make here is the
15 agreement to buy lateral, so it's between an individual
16 manufacturer and the country. So, in the very tight
17 timelines that we have for influenza, it's very
18 difficult to meet those timelines if we have to
19 negotiate prior informed consent and mutually agreed
20 terms in a matter of months.

21 So, the current situation is that an

1 increasing number of countries have enacted
2 legislation, whether that's a national legislation or
3 Nagoya Protocol legislation, and in many cases this
4 does include genetic sequence data. I have to say that
5 most of the national influenza centers have continued
6 to supply influenza viruses under their agreed terms of
7 reference as part of the global influenza surveillance
8 and response system, or GISRS, however, there's often a
9 lack of legal clarity if the viruses can be used for
10 vaccine manufacturing research or any commercial
11 purposes. And this is having a big impact on our
12 ability to use some of the candidate vaccine viruses
13 and since September 2018, we've had in excess of 30
14 influenza viruses impacted by this type of legislation.
15 I think we're up to 37 now.

16 And the graphic on the right-hand side here
17 just shows, I know you can't read all the viruses
18 impacted, but it just shows you which viruses we've got
19 authorization to use, which we had tacit authorization
20 to use, which required material transfer agreements,
21 and then, the viruses listed on the right-hand side

1 with the red boxes are viruses that we never received
2 authorization to use. And some of those are older
3 viruses, but some, the top ones are more recent
4 viruses. And, basically, we timeout if we don't get
5 the authorization within a certain period of time.
6 It's too late for the season and then, later on, the
7 virus has moved on and so, some of these viruses become
8 irrelevant.

9 But we had a particular issue for this
10 Northern Hemisphere when the virus from Cambodia was
11 recommended. There were delays in obtaining legal
12 clarity on the ability for us to use the A/Cambodia for
13 commercial purposes. Permission was given for non-
14 commercial purposes, and it took about a month after
15 the WHO recommendation to get clarity that this could
16 be used in manufacturing. And this had a big impact on
17 manufacturers because it impacted the timing of the
18 decision of which viruses would be used by each
19 manufacturer. It also called into question whether
20 critical reagents would be prepared and made available
21 to manufacturers. So, even if a manufacturer went

1 ahead and used the Cambodia strain, there was a period
2 of time that we weren't sure whether the critical
3 reagents would be prepared to support that.

4 And it was a very difficult situation, but the
5 virus that was listed on the WHO website couldn't
6 actually be used by manufacturers and we didn't get
7 that clarity for, until a month later. And there was a
8 possibility that manufacturers would have to change the
9 strain that they used, and the possibility of batches
10 being discarded. In one particular case, there was one
11 example of a vaccine manufacturer that chose an
12 alternative strain, but fortunately there was an
13 alternative strain, from Tasmania, but the yields on
14 some manufacturing platforms were lower and one
15 particular manufacturer supplied 40 percent less
16 vaccine doses because they had made the decision, a
17 safe decision, if you like, not to have legal
18 uncertainty, but it resulted in fewer doses being
19 supplied to the market.

20 We did, as I said, eventually get approval
21 from Cambodia for commercial use, but there is still no

1 written confirmation that no benefits are required.
2 And in some countries where the legislation is now
3 being enforced, it's very difficult for us to provide
4 evidence that we have met all the requirements. So
5 this does pose an ongoing risk to seasonal influenza
6 vaccine supply, including for the U.S. market. So it's
7 something that we have to be vigilant monitoring, but
8 also try to improve the situation.

9 There have been frequent questions regarding
10 the compliance of Nagoya Protocol on sharing the
11 seasonal influenza viruses and often different
12 stakeholders are facing similar issues. So the legal
13 firm Covingtons, based in Belgium, the Belgium office,
14 generates a report on the impact of Nagoya Protocol on
15 seasonal influenza virus sharing based on interviews
16 that they carried out with stakeholders. And this was
17 done last year. And it included the current work
18 processes in GISRS, the impact of Nagoya Protocol on
19 national ABS laws, and some suggestions to overcome the
20 challenges that we're currently facing. And the report
21 was reviewed by a multi-stakeholder group at a meeting

1 held at NIBSC in the UK last July, with the aim of
2 finding solutions to some of these Nagoya challenges,
3 specifically for influenza.

4 And there's a general agreement to work
5 towards a common approach to compliance with the Nagoya
6 Protocol and national ABS laws. And we discussed this
7 again at the January NIBSC meeting earlier this year.
8 And we agreed to look at continuing communication with
9 national authorities, particularly the Ministries of
10 Health and Environment, because they're the ones that
11 the Nagoya Protocol (inaudible). So they're the
12 ministry that are involved in this type of legislation.

13 And to really have the benefits of the GISRS
14 system recognized and see how that fits with the
15 benefit systems in the Nagoya Protocol. WHO are also
16 in the process of developing a toolkit for the National
17 Influenza Centers to use with their Nagoya Protocol
18 National Focal Points, trying to explain how the GISRS
19 system works and to recognize the benefits that GISRS
20 brings to the individual countries, and to try and have
21 those benefits recognized under the legislation.

1 There is also something called the Seasonal
2 Influenza Material Transfer Agreement that has been
3 used in some cases, we're looking to see if that could
4 be used more broadly. And, then, a review of the Terms
5 of Reference for the National Influenza Centers. So
6 these are things that we think that we can, that deal
7 specifically with influenza that might ease the
8 situation. Well, I guess our message today is that the
9 bedrock of global health security is the swift,
10 certain, and unencumbered access to pathogens and their
11 genetic information. And I think this has been talked
12 about a lot because of the COVID-19 pandemic. A lot of
13 the things that are being discussed and lessons learned
14 are all talking about rapid sharing of pathogens and
15 their genetic information. And pathogens know no
16 borders, it's not like a plant that's growing in a
17 country. For me, I think of pathogens as tourists
18 passing through countries, so putting a border around a
19 pathogen and accessing the benefits is very difficult.
20 And sometimes it won't be easy to say that the pathogen
21 started in that particular country. The timely sharing

1 of samples and genetic information is absolutely
2 essential if we're going to respond to potential
3 epidemics and pandemics.

4 And the inclusion of pathogens, including
5 influenza, under this national ABS legislation is
6 already causing significant delays and disruptions. As
7 I said before, the bilateral negotiation approach is
8 just time consuming, and we simply don't have the time
9 when we're trying to respond to some of these public
10 health emergencies. And legal certainty regarding the
11 status of pathogen sharing under ABS legislation is
12 necessary and we feel that clear exemption of pathogens
13 will be the most effective way forward, but as
14 negotiations are going on and the landscape complexity
15 is increasing, we're not sure if that's going to be a
16 possibility. There are a number of things being
17 discussed that impact the access and benefit sharing.
18 We have the PIP Framework for pandemic influenza, which
19 there's talk about that being expanded. Currently it
20 just covers (inaudible) samples, that could be expanded
21 to cover genetic sequence data.

1 We have the Nagoya Protocol and there is a big
2 discussion whether digital sequence information or
3 genetic sequence data is included under that. And
4 there are discussions going on in Geneva later in March
5 to prepare for a big meeting later this year, the
6 COP15, where that will be discussed specifically. The
7 WHO is looking to BioHub system, which would be
8 physical samples of pathogens, and there is an access
9 and benefit sharing element to that. And then there's
10 also discussions started on developing an international
11 treaty on pandemics or an international instrument.
12 And, again, there is an ABS element to that. And this
13 causes concern because we want an unencumbered supply
14 of pathogens as quickly as possible. And in order for
15 us to achieve this 100 day mission that was discussed
16 by the G7, the ABS legislation is not going to help
17 with that if it causes delays in the sharing of
18 pathogens.

19 So, in summary, I just wanted to spend the
20 time on Nagoya so that people understand how serious
21 this is, not just for influenza, but it particularly

1 impacts it because we change the vaccine every season.
2 So, in summary, so the current Northern Hemisphere
3 season, despite extremely low circulation of influenza
4 viruses, the viruses continue to evolve. Which
5 resulted in the vaccine composition being updated and
6 there were two changes. The great news was that the
7 CVV's and potency assay reagents were supplied within
8 normal the timeframes, despite some of the challenges
9 we were still facing due to COVID. We did have some
10 issues with supply, materials, and components, and some
11 issues with transport and freight, but in the end we
12 were able to work around those. Approximately 174
13 million influenza vaccine doses were supplied to the
14 U.S. market, but the vaccine uptake rates were slower
15 and lower than the last two seasons.

16 Influenza is a serious and, yet, often
17 underestimated disease for which vaccination is the
18 best means of protection. So we certainly want to
19 maintain and increase vaccination rates to provide
20 protection against this disease. The Nagoya Protocol
21 and ABS legislation is continuing to pose challenges

1 and increasing challenges, and it impacts our ability
2 to select and manufacture the best vaccine strains.
3 And as I just said, the complexity of that ABS
4 landscape is increasing and we're worried about further
5 delays, but also, a sort of slacking of obligations as
6 well, which might cause even more delays. And flu
7 vaccination continues to be of great importance as the
8 flu circulation increases and international travel
9 resumes.

10 And I just want to finish on the teamwork
11 theme. Again, so teamwork is needed to get the
12 influenza vaccine over the finish line. And that
13 includes getting people vaccinated. So in the interest
14 of public health, the focus on the COVID-19
15 vaccinations must not negatively impact other
16 vaccinations, including influenza. Thank you for your
17 attention. Thank you.

18

19

Q AND A SESSION

20

21

DR. HANA EL SAHLY: (Audio skip) pertaining a

1 significant uptick in influenza vaccine uptake in the
2 fifth year of the pandemic. It went back, the average,
3 I guess, after the first year, the second year of the
4 pandemic. Is that a global phenomenon from your
5 perspective, you know, from what you have seen?

6 **DR. BEVERLY TAYLOR:** A number of countries, a
7 similar picture. And I think so much focus has been on
8 COVID-19, and I don't want to get into all the reasons
9 and everything, but there's talk of vaccine fatigue
10 because everybody has had (audio skip). Some people
11 think if they've had the COVID-19 vaccine, they no
12 longer need to get the flu vaccine. The low flu
13 circulation may have made some people think that they
14 no longer need the vaccination rate. I think a lot is
15 due to messaging as well. I have to say, I mean, I'm
16 based in the U.K., the U.K. rates have not seen the
17 same decline. But I think there was a real push for
18 both vaccinations over the winter months, so the
19 general picture, I think, is that flu vaccinations have
20 reduced compared to last year, certainly.

21 **DR. HANA EL SAHLY:** Right, any of my committee

1 colleagues with questions? I see one hand raised, two
2 hands raised. So, Dr. Annunziato and Dr. Chatterjee.
3 Beginning with Dr. Annunziato.

4 **DR. PAULA ANNUNZIATO:** Thank you. So I wanted
5 to thank Dr. Taylor for those very clear and
6 comprehensive comments on what it takes in order to get
7 flu vaccines, really lifesaving flu vaccines to the
8 world each year. I also wanted to comment so that the
9 public and this committee understands that the concerns
10 around the Nagoya Protocol and its potential to be a
11 barrier for future effective responses to pandemics, is
12 actually a concern that I believe all vaccine
13 manufacturers share. Even those that do not work in
14 the influenza space. And I think is a concern for many
15 people who are working in this area of health security
16 and pandemic response. So I wanted to reiterate that.

17 And, then, I also would note, the question
18 came up around the trends of the influenza vaccine
19 uptake in the United States during this past season,
20 that it's my understand, and perhaps Dr. Cohn actually
21 could comment on this as well if she's available on the

1 line, that in the United States, in fact, a number of
2 vaccines have seen a drop-off since the COVID pandemic,
3 in vaccine uptake. So this is a concern, actually I
4 think for our entire population in terms of vaccine
5 preventable diseases and having good protection. And
6 bringing that health benefit to the people of the
7 United States. But thank you very much.

8 **DR. BEVERLY TAYLOR:** Thank you.

9 **DR. HANA EL SAHLY:** Thank you, Dr. Annunziato.
10 Dr. Chatterjee.

11 **DR. ARCHANA CHATTERJEE:** Yes, thank you very
12 much, Dr. Taylor, for your presentation. I'm not
13 certain whether you are able to answer this question or
14 not, but the question did come to my mind and perhaps
15 some of our FDA colleagues who are on the call could
16 also weigh-in. And that is with regard to the newer
17 platforms, particularly the mRNA-based platforms that
18 are being developed for influenza vaccines, for other
19 vaccines too, but specifically for influenza vaccines,
20 and the combination vaccines of COVID-19 and influenza.
21 Are there discussions among the vaccine manufacturers

1 about how those would be incorporated into the
2 available vaccines or is that too early yet to have
3 those discussions?

4 **DR. BEVERLY TAYLOR:** I think, as an industry
5 group we certainly researched it. A number of our
6 companies are looking at new -- can you hear me? I'm
7 getting strange messages. Yeah. So we have proven
8 technologies for influenza vaccine manufacturing, and I
9 think the new technologies are extremely exciting, but
10 they still need to be proven for influenza. So, for
11 example, if we had the pandemic today, influenza
12 pandemic, we would still be heavily reliant on the
13 proven technologies that we have today. But we
14 certainly have been thinking about the new technologies
15 and how we involve some of the newer companies in
16 discussions around influenza and also things like
17 Nagoya Protocol. Because a lot of the new
18 technologies, the actual production bit is different,
19 but all the supporting things around it, like getting
20 your license and things that could impact it like
21 Nagoya Protocol, they will face the same challenges as

1 the existing technologies, so we don't want to lose an
2 advantage or something new if it gets bogged down in
3 the same issues. So we still need to address these
4 other issues. Not just the manufacturing process
5 itself. Did I answer your question?

6 **DR. ARCHANA CHATTERJEE:** Yes, you did. Thank
7 you.

8 **DR. HANA EL SAHLY:** Thank you. (Audio skip).

9 **MR. MICHAEL KAWCZYNSKI:** All right, again,
10 thank you all for that portion of today's meeting. And
11 it is now time for our lunch break. We're going to
12 take, looking at the time, about 45 minutes. We'll
13 make it a little bit more than that, so that we're
14 going to reconvene at 1:45, actually, no, we're going
15 to reconvene at 1:30. So see you all back then.
16 That'll be 1:30 Eastern Time. About 37 minutes.

17

18 **[LUNCH BREAK]**

19

20 **OPEN PUBLIC HEARING**

21

1 **MR. MICHAEL KAWCZYNSKI:** Okay, welcome back
2 from our lunch break and to the 171st Vaccines and
3 Related Biological Products Advisory Committee Meeting
4 on Influenza. Let's get started and I'm going to hand
5 it back over to our chair, Dr. El Sahly, take it away.

6 **DR. HANA EL SAHLY:** Thank you, Michael. Our
7 next section of the meeting is for the Open Public
8 Hearing session. I want to welcome you all to the Open
9 Public Hearing Session. Please note that both the Food
10 and Drug Administration, and the public, believe in a
11 transparent process for information gathering and
12 decision making. To ensure such transparency at the
13 Open Public Hearing session of the Advisory Committee
14 Meeting, the FDA believes that it is important to
15 understand the context of an individual's presentation.

16 For this reason, FDA encourages you, the Open
17 Public Hearing Speaker, at the beginning of your
18 written or oral statement to advise the Committee of
19 any financial relationships that you may have with the
20 sponsor, its product and if known, it's direct
21 competitors. Samples of this financial information may

1 include sponsors payments of expenses in connection
2 with your participation in this meeting. Likewise, the
3 FDA encourages you at the beginning of your statement
4 to advise the Committee if you do not have any such
5 financial relationships. If you choose not to address
6 this issue of financial relationships at the beginning
7 of your statement, it will not preclude you from
8 speaking. So I think we have one OPH speaker. Go
9 ahead.

10 **DR. PRABHAKARA ATREYA:** This is Prabha Atreya,
11 thank you, Dr. El Sahly. Before I begin calling the
12 designated speaker, I would like to just add the
13 following items from FDA. FDA encourages participation
14 from all public stakeholders in the decision making
15 process. Every Advisory Committee Meeting includes an
16 Open Public Hearing session during which interested
17 participants may present relevant information or views.
18 Participants during their OPH session are not FDA
19 employees or members of this committee.

20 FDA OPH speakers may represent a range of
21 viewpoints. The statements during this Open Public

1 Hearing session reflect the viewpoints of the
2 individual speakers or of their organization but are
3 not meant to indicate agencies agreement with the
4 statements made. So, with that guidance, I would like
5 to call upon Ms. Sarah Barry, who is listed to speak at
6 this OPH session. Thank you. Ms. Barry, you can go
7 ahead now.

8 **MS. SARAH BARRY:** Hello, can you hear me?

9 **DR. PRABHAKARA ATREYA:** Yes, very much.

10 **MS. SARAH BARRY:** All right, thank you very
11 much. And thank you sincerely members of the Vaccine
12 and Related Biological Products Advisory Committee. My
13 name is Sarah Barry and I'm the new director of
14 research and media relations for the SAFE Communities
15 Coalition and I have no financial conflicts of
16 interest. I continue to be humbled by the detailed and
17 transparent discussions that have been had today. My
18 goal is to make sure that your work, the research, the
19 surveillance, the analyses, are not hindered by poor
20 public health legislation. Next slide, please.

21 The SAFE Communities Coalition builds

1 grassroots coalitions, advocates for legislation, and
2 educates the public about our pro-science message. We
3 partner with family foundations, individuals, and other
4 donors to build as broad a pro-science community as
5 possible in states across the country. Next slide,
6 please. We want to help you communicate science-based
7 recommendations to policy makers, such as those that
8 have been discussed at the committee today. We have
9 found significant evidence that anti-vaccination
10 activists are working directly with state politicians
11 to undermine anything to do with vaccination, and that
12 undeniably will include any recommendations made by the
13 committee.

14 To help put these anti-vax influence into
15 perspective, I'll be sharing a few pieces of research
16 that we are releasing as an interim report. Next
17 slide, please. So, as you can see on this slide, and I
18 will say out loud for anybody who is vision impaired,
19 we have 22 out of 50 states with anti-vaccination
20 groups, 9 out of 50 states with anti-vaccination
21 501c4s, that's a registered political lobbying group.

1 Five out of 50 states with anti-vaccination PAC's, 20
2 out of 50 states with active pages on Facebook, and 12
3 out of 50 states with more than one activist group.
4 And as our analysis continues, again, this is an
5 interim report, it would be wise to expect that these
6 numbers will increase significantly.

7 We wanted to get a better idea of how many
8 states, obviously, again, have these groups. And a
9 byproduct of that research was both the reminder that
10 Facebook has continued to be an integral platform for
11 the anti-vaccination community, and, again, a stark
12 realization that it was actually very common for states
13 to have multiple groups, sometimes even going beyond
14 three or four groups in an individual state. I am from
15 Ohio, and I have done a lot of awareness about this in
16 Ohio, and we have at least two groups in Ohio, and one
17 of them is considering an anti-vaccination PAC. Next
18 slide, please.

19 So anti-vax legislation before the pandemic,
20 flu vaccines were the target. Laws that were written
21 about flu vaccine mandates have almost near identical

1 language to recent legislation regarding COVID vaccine
2 mandates. And they feel safe recycling these arguments
3 because the specific influence anti-vaccination
4 activists have had on state politics went largely
5 unnoticed. Next slide, please. Anti-vaccine PACs,
6 it's important to note that many of these groups will
7 not refer to them, obviously, under the term of anti-
8 vaccine. They're branded as medical freedom or health
9 freedom.

10 This is very important to note because it's a
11 distancing tactic. They understand that the public
12 perception of anti-vaccination attitudes is not in
13 their favor and they're taking advantage of that by
14 branding them as something else. Over the past few
15 election cycles we have found hundreds of thousands of
16 dollars raised and spent for anti-vaccine political
17 purposes. And we also have evidence, again, that more
18 PACs are imminent because they feel emboldened at the
19 current lack of opposition to their PACs. Next slide,
20 please.

21 Dr. Beverly Taylor made an excellent relay

1 race analogy in her presentation concerning the
2 distribution of influenza vaccines. The legislative
3 topics that I've been talking about are just additional
4 hurdles in that relay race analogy. And, again, my
5 goal is simple, it's to make sure that you all, the
6 scientific community, the evidence-based community,
7 knows the full extent of those hurdles within the
8 United States so that your work is not wasted. Even
9 more so beyond just simple hurdles, wouldn't it just
10 suck to get to the end of the finish line and see local
11 politicians taking the baton out of your hand and
12 pushing you down on the ground.

13 And that is what I see as a very likelihood
14 happening if the influence of these anti-vaccination
15 lobbying groups are not addressed and at least
16 understood, even if you don't call them out, at least
17 having an awareness of what they're operating and the
18 full extent, that is what is crucial. And that is my
19 presentation, and we welcome any questions at this
20 time. Thank you. Hello?

21 **DR. HANA EL SAHLY:** Well, I don't see any

1 raised hands for questions.

2 **DR. PRABHAKARA ATREYA:** Right. We will not
3 take any questions at this time and since she's the
4 only pre-registered OPH speaker, I think that concludes
5 the OPH session. And then, in the interest of time, we
6 can move forward with the next time item on the part of
7 the session today. Thank you, Ms. Barry.

8

9 **COMMITTEE DISCUSSION, RECOMMENDATIONS, AND VOTE**

10

11 **DR. HANA EL SAHLY:** Thank you, Prabha. So we
12 will be voting shortly on the new vaccine for the
13 upcoming season in the Northern Hemisphere. The data
14 we saw today point to a season of low circulation for
15 influenza virus in general. A little more than first
16 year of the pandemic, nonetheless we had still very few
17 data to go by. There's indications that potentially
18 there is an uptick in late February, but that remains
19 to be seen on how it will evolve and whether it will
20 wind down soon. It was largely an H3N2 season for the
21 U.S., with globally a mismatch between the Northern

1 Hemisphere flu strain selective H3N2, the ones
2 circulating we heard that the VE estimate is somewhere
3 that is in the 15 to 18 percent we saw. But it was
4 very wide confidence interval, pointing to a range
5 potentially in this estimate.

6 And we did not see data on the impact on the
7 sheer outcomes of disease, which previous seasons are
8 any indicators, usually that outcome -- the efficacy
9 against that particular outcome would be a bit higher.
10 So, two strains are projected to be , the H1N1 and the
11 H3N2. We heard that the reagents are available for
12 cell-based and egg-based products. And I don't see any
13 particular concerns.

14 The only thing that comes to mind is the
15 declining (audio skip) and the issue of the Yamagata,
16 which I think is too early to make any determination.
17 It's two years' worth (audio skip) and their impact on
18 all viral (audio skip).

19 So I invite my committee members to raise
20 their hands in Adobe and if you like to make a comment,
21 ask a question to David Wentworth. I see three raised

1 hands, we begin with Dr. Hank Bernstein.

2 **DR. HENRY BERNSTEIN:** Yeah, thank you. I was
3 wondering what (audio skip) virus. Dr. Wentworth,
4 you've noted the response to the 5A.1 virus subclade
5 for the 6B.1A in 6 to 35 month old's was quite
6 suboptimal. I mean, it seemed quite poor. Would this
7 suggest the need for us to consider a change in the
8 H1N1 vaccine strain?

9 **DR. DAVID WENTWORTH:** Yeah, I appreciate that
10 question, and that's partly why I showed that data.
11 With the pediatric population, H1N1 can be severe and
12 so, it's a very important population to cover. The
13 issue is two-fold. One, it's quite uncertain whether
14 it's going to be a 5A.2 or a 5A.1 influenza season
15 coming forward in the H1N1 season. So, for example, in
16 2022 and 2023, it could be a bit of a mixture. It
17 could be 5A.1 most likely with that 155 substitute,
18 which would be further advanced. Because the old
19 5A.1s, they've really been around since before we
20 changed the vaccine to a 5A.2, so the preponderance of
21 them in the United States community I think is going to

1 be quite low.

2 And that's partly why the 5A.2 vaccine was
3 selected because we know it cross-protects against the
4 5A.1. Now, if you protect all of the adults, and the
5 older pediatrics, say 3 to 17, actually that middle
6 range in pediatrics, because they were around in the
7 2009 pandemic, have the least burden and the highest
8 titer. So if they get vaccinated, they have a very low
9 likelihood of transmitting it to, say, a younger
10 sibling that may be in that very early window of age.
11 And, so, all of those considerations were made in the
12 BCM process at the WHO meeting, and so really we have
13 one cohort in that age range that's the most
14 susceptible to this other strain.

15 But they would also be the most susceptible to
16 5A.2s, which are more likely to predominate. They have
17 more an antigenic advance coming out of India, so those
18 additional ones, like I showed you that India Punay
19 (phonetic) used in our serology studies, that is the
20 most antigenically advanced 5A.2 virus. It's the most
21 antigenically advanced H1 virus. And, so, when you

1 consider our population as a whole in the United States
2 in particular, we've seen quite a bit of the 5A.1s
3 prior to the pandemic. And vaccinated against the
4 5A.1s, and our first vaccination against 5A.2s occurred
5 in this particular season, the 2021-'22 season. And
6 the big recommendation was to not go forward into a
7 more advanced 5A.2 vaccine virus, because that didn't
8 appear warranted based on the serology studies and the
9 antigenicity studies.

10 And, so, really it's a matter of that very
11 small sliver of our population versus the entire
12 population. And by protecting the entire population,
13 we may protect that small sliver. What we would
14 communicate very heavily, both through the ACIP and
15 through position networks, *et cetera* was if we started
16 to see a 5A.1 season, this would be something we would
17 communicate that treatment is advisable for that very,
18 pediatric population. Test early, treat early. And,
19 so, that's the logic behind the recommendation. I hope
20 that addresses it.

21 **DR. HENRY BERNSTEIN:** Yes, thank you.

1 **DR. HANA EL SAHLY:** Dr. Offit?

2 **DR. PAUL OFFIT:** Right, thank you. So, David,
3 I have a question that's sort of a follow up to Hana's
4 earlier question. Regarding the importance of
5 neuraminidase, and considering neuraminidase, we make
6 these decisions. We now have a fair amount of
7 experience with FluBlok, which only contains the
8 hemagglutinin. Has that educated to any extent about
9 the importance of paying attention to neuraminidases as
10 we're creating these strands?

11 **DR. DAVID WENTWORTH:** Yeah, so far it really
12 hasn't educated us that much about it. And I would
13 tell you there's a couple of reasons we need to think
14 about that from a group like this, that you need to
15 think about it, and contribute your ideas to even the
16 regulatory community. One, the FluBlok uses 45
17 micrograms of antigen, so it's uses three times more
18 antigen than an egg-based or cell-based vaccine. So
19 that's one difference. And then it doesn't have NA.
20 We don't have, as far as I'm aware, there are not
21 platform specific VE studies that have been completed

1 yet. In part because of the pure market share of the
2 different vaccines (audio skip) are much lower
3 prevalent, like the cell-based now is getting up to 30-
4 40 million doses.

5 And I don't know off the top of my head what
6 FluBlok is. But that is something that I think is
7 needed either, maybe even in RCTs or some other type of
8 study. You know, test-negative design won't capture
9 something like FluBlok difference from cell-based or
10 egg-based.

11 The other thing I would say is that comparison
12 may be difficult because we do not require a specific
13 quantity of NA in the vaccines that could have NA. So
14 we're relying solely on co-purification of the NA in a
15 process (audio skip). The thing that is tracked in the
16 purification process is the hemagglutinin.

17 So if you're a vaccine manufacturer, are you
18 going to change a process because you're reducing the
19 NA that's co-purifying it, or are you only going to
20 change a process if your HA is going down or up, right?
21 So I think some of the incentives that a manufacturer

1 may have are purely on the HA and the NA is there by
2 happenstance. And if you just, at the very first
3 purification step of an influenza virus particle,
4 generally, this is a little bit of a generality, but
5 they'll be one quarter the NA as HA because there's
6 about 100 neuraminidase molecules on the surface of a
7 particle and 4 to 600 hemagglutinins.

8 And, so, just by doing that stoichiometry,
9 you're always going to have, so a quarter of the amount
10 of NA antigen in the, and then you're depending on co-
11 purification of that. And, so some of this may come to
12 light with new vaccines as well, Dr. Offit. If people
13 using recombinant approaches or DNA, RNA approaches
14 decide to start putting those in at equal molar levels,
15 I think they could be a big benefit. It could be a big
16 benefit to mitigate drift in the, we see drift in both
17 the HA and NA, so clearly the NAs the target of our
18 immune system, and clearly the NA antibodies won't
19 protect us from infection, but they will protect from
20 dissemination of the infection. So they block, it acts
21 just like a neuraminidase inhibitor blocking the

1 activity of that enzyme.

2 And they, of course, can do antibody-dependent
3 cellular cytotoxicity, CTLs, all of that. And, so,
4 it's a long-winded answer that says I don't know, so I
5 apologize for that. But I am thinking along the lines
6 I think of many in this committee where we would like
7 to see NA be more of a part of a holistic flu vaccine.
8 But we don't know from FluBlok yet if it's told us
9 anything.

10 **DR. PAUL OFFIT:** Thanks, David.

11 **DR. HANA EL SAHLY:** We have two additional
12 raised hands. Beginning with Dr. Berger.

13 **DR. ADAM BERGER:** Hi. Thanks very much and
14 this should just be a pretty quick, clarifying
15 question. I just wanted to ask about the Yamagata
16 strains that were detected, or reported, I guess. You
17 had mentioned in your talk that there were 13 and
18 Commander Gustin had reported that they had actually
19 identified one. I just wanted to make sure there
20 wasn't overlap there. The one from DoD is not included
21 in the 13 that you had actually screened, correct?

1 **DR. DAVID WENTWORTH:** Well, I actually don't
2 know. I was going to circle back with him, maybe he's
3 on and he knows whether or not they investigated that
4 further. Like I said, there's a big iceberg and we
5 want to track down any that are potentials. One that I
6 know of that was tracked down by the collaborating
7 center in Crick, had the exact same sequence as a live
8 attenuated vaccine B/Phuket/HA, so that one we're
9 pretty confident was a false Yamagata identification by
10 PCR.

11 **DR. ADAM BERGER:** Thanks, that's where I was
12 trying to get an understanding. It's just the
13 detection problem or --

14 **DR. DAVID WENTWORTH:** Yeah, I'm sorry I don't
15 have a better answer. I will circle back and see if
16 that's in the 13 or if it's a 14th that maybe we want
17 to investigate further.

18 **DR. ADAM BERGER:** Thank you.

19 **DR. HANA EL SAHLY:** And Dr. Monto.

20 **DR. ARNOLD MONTA:** Thank you.

21 **DR. DAVID WENTWORTH:** The Emeritus Professor

1 now.

2 **DR. ARNOLD MONTO:** Hello. Yes. But still
3 working on VE studies.

4 **DR. DAVID WENTWORTH:** Yeah.

5 **DR. ARNOLD MONTO:** I want to commend you for
6 all the work you are doing with strain selection. And
7 acknowledge the frustration we all feel about next
8 years, we had a question about the choice of the H1N1,
9 I remember, in 2019. 2020, we had H1N1 viruses that
10 some of them were susceptible to the vaccine, protected
11 by the vaccine, and some were not. Also, I've been
12 reviewing the Southern Hemisphere recommendations and
13 the subsequent Northern Hemisphere recommendations and
14 it's very clear that five years out of the last ten, I
15 believe, the correction of the Northern Hemisphere
16 recommendation by later evidence was put into the
17 Southern Hemisphere vaccine recommendation.

18 Which then became the Northern Hemisphere
19 recommendation for the next year. And this is sort of
20 trying to catch up when you can't catch up in the
21 process. And I just want to make an appeal that after

1 we've been busy with COVID for the last couple of
2 years, we not forget the universal influenza vaccine
3 programs which were started to try to get us out of
4 this situation, which a new terminology, which I
5 prefer, is super seasonal.

6 We need super seasonal vaccines so that we
7 don't live with this kind of catching your tail
8 situation, which I think is inevitable no matter how
9 careful you go through the strain selections. So just
10 a comment and appreciating your frustration with this,
11 and in test negative studies and all the rest, so thank
12 you.

13 **DR. DAVID WENTWORTH:** Thank you very much,
14 Dr. Monto, what I've done pales in comparison to what
15 you've done and so, I'm continually impressed by all
16 the studies and all of the work in Michigan. It's such
17 a tremendous team of investigators there. I do also --
18 chronically, I share your frustration with not having
19 the data in time to, so, for example, the Southern
20 Hemisphere recommendation, (audio skip) vaccine virus
21 was isolated about a couple weeks after our meeting

1 here. And then, of course, it takes about three months
2 to develop it as a vaccine virus, right? So first you
3 have to isolate it, then you have to do the analysis
4 with (inaudible) and things like that to understand
5 it's a good antigen.

6 And then you have to get it into the
7 reassortant labs and do the analysis of those vaccine
8 viruses and their gross properties in cell-based
9 vaccines and in egg-based vaccines. Really before it
10 can be nominated as a vaccine, and the baton, you have
11 to hand the baton to a manufacturer. You can't say,
12 this is the one we would like, right? All of us share
13 that frustration. And I think the other thing that's
14 underappreciated that I tried to do in this particular
15 presentation, was to show and mitigate the drift. And
16 H3N2 is the fastest drifting virus. Other things we
17 can do to mitigate the drift, we just talked about
18 neuraminidase. Another thing, I am very involved in
19 the COVID response and the COVID vaccines, and what you
20 may not appreciate in whole sets of data, is the titers
21 for a COVID vaccine are (audio skip) they're not in the

1 hundreds. So the neutralizing titers are in the
2 thousands.

3 We could go a long ways to mitigate drift by
4 having higher titer produced from our vaccine. And so
5 that's a, it's a little bit different, I've been trying
6 to always get in front of antigenic evolution, which at
7 any moment in time is a snapshot, right? We can take a
8 picture right now and I can tell you right now (audio
9 skip) that I'm worried about that one went to 192, you
10 know, the 53N and the 53G, the Maryland-like one. And
11 what we already (audio skip) 1A, they could easily have
12 emerged in the 2a2 vaccine, like if we went on with a
13 Bangladesh vaccine, which would have been the only
14 choice at the time, then that would have only protected
15 against (audio skip) not against Cambodia-like viruses,
16 which occur now and then, and not against the other
17 clades.

18 So, I don't know, you gave me an opportunity
19 to talk to you about it, but I wish we made decisions
20 every couple of months, and we'd probably be in a
21 little bit better shape. He does a fantastic job

1 looking at all the data, being critical, and I do think
2 one thing that's really underappreciated is stepping
3 forward does improve our VE. It's just hard to see.
4 And I can clearly see it with the immune, the serum.
5 That's a more direct measure.

6 **DR. ARNOLD MONTO:** Thank you.

7 **DR. HANA EL SAHLY:** I do not see any more
8 questions or comments from the committee judging by no
9 raised hands. With that we probably need to move to
10 voting part of the meeting. Dr. Atreya?

11 **DR. PRABHAKARA ATREYA:** Yes, thank you. Dr. El
12 Sahly. The voting will be done, I think we're going to
13 be projecting the voting questions and then there will
14 be one voting question from that, and then we will vote
15 on each question separately. And Christina Vert,
16 Michael therefore will be conducting the voting
17 process, she'll have some instructions then followed by
18 the voting. So, Christina, you want to start and Mike,
19 do you want to present the voting questions on the
20 screen please?

21 **MR. MICHAEL KAWCZYNSKI:** Okay.

1 **MS. CHRISTINA VERT:** Thank you. I will go
2 ahead and describe the voting process. Only our
3 members and temporary voting members will be voting at
4 today's meeting. With regards to the voting process,
5 Dr. El Sahly will read the final questions for the
6 record and afterwards, all members and temporary voting
7 members will cast their vote by selecting one of the
8 voting options, which include yes, no, or abstain. You
9 will have two minutes to cast your vote after the
10 question is read.

11 And please note that once you have cast your
12 vote you may change your vote within the two minute
13 timeframe, however, once the poll has closed all votes
14 will be considered final. Once all the votes have been
15 placed, we will broadcast the results and read the
16 individual votes aloud for the record. And does anyone
17 have any questions before we begin? Okay, I don't see
18 any questions. Okay, Dr. El Sahly, if you could please
19 read the voting question?

20 **DR. HANA EL SAHLY:** Question one: For the
21 influenza A (H1N1) component of the 2022-2023 influenza

1 virus vaccines in the U.S., does the committee
2 recommend: A/Victoria/2570/2019 (H1N1) pandemic 09-like
3 virus for the egg-based vaccines; A/Wisconsin/588/2019
4 (H1N1) pm09-kuje virus (Cell- or recombinant-based
5 vaccines)?

6 **MS. CHRISTINA VERT:** Okay, at this time, you
7 may vote, and we'll start the timer at two minutes.

8 **MR. MICHAEL KAWCZYNSKI:** Just a reminder to
9 voting members that at the bottom of your screen, dead
10 center, you will see the voting question. Again, you
11 have the option of yes, no, or abstain. There is no
12 submit button, just pick whichever you prefer. We have
13 about one more minute for you to make your selection.

14 **MS. CHRISTINA VERT:** Okay, it looks like all
15 the votes are in. And at this time the two minutes are
16 up. And, so, Michael if you could please end the vote
17 by closing the poll? Okay. Okay, there are 11 total
18 voting members for this particular vote, the vote is
19 unanimous, 11 out of 11 votes.

20 **DR. PRABHAKARA ATREYA:** Mike, do you want to
21 broadcast the results please?

1 **MR. MICHAEL KAWCZYNSKI:** The votes are
2 broadcast.

3 **DR. PRABHAKARA ATREYA:** Okay, thank you.

4 **MR. MICHAEL KAWCZYNSKI:** You have to read the
5 names if you'd like.

6 **MS. CHRISTINA VERT:** Yes, I'm going to go
7 ahead and now read the names. Dr. Berger, yes. Dr.
8 Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes. Dr.
9 Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes. Dr.
10 Bernstein, yes. Dr. James, yes. Dr. Portnoy, yes.
11 Dr. Offit, yes. Okay, so I am done with that vote, and
12 I will pass this back over to Dr. El Sahly.

13 **DR. HANA EL SAHLY:** Question two: For the
14 influenza A (H3N2) component of the 2022-2023 influenza
15 virus vaccine in the U.S., does the committee recommend
16 an A/Darwin/9/2021 (H3N2)-like virus for the egg-based
17 vaccines; an A/Darwin/6/2021 (H3N2)-like virus (cell-
18 or recombinant-based vaccines)? Vote yes, no, abstain.

19 **MS. CHRISTINA VERT:** Thank you. Go ahead and
20 vote. We start the two minutes, again, at this point.
21 All right. The voting's almost done. Looks like all

1 the votes are in. We can go ahead and end the poll.
2 Okay. Again, we have a unanimous vote, 11 out of 11
3 voting yes. And I will go ahead and read the votes.
4 Okay. All right I'm going to go ahead, oh, wait a
5 minute. Give me a minute. Okay. Michael, did you end
6 the poll? Poll closed, okay. I'll go ahead and read
7 the votes. Dr. Berger, yes. Dr. Shane, yes. Dr.
8 Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr.
9 Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes.
10 Dr. James, yes, and Dr. Portnoy, yes. Dr. Offit, yes.
11 And that concludes my reading of the results for the
12 second vote. I will hand it back over to Dr. El Sahly.

13 **DR. HANA EL SAHLY:** Question three: For the
14 influenza B component of the 2022-2023 trivalent and
15 quadrivalent influenza virus vaccines in the U.S., does
16 the committee recommend inclusion of a
17 B/Austria/1359417/2021-like virus for B/Victoria
18 lineage? Vote please yes, no, or abstain.

19 **MS. CHRISTINA VERT:** Okay, at this time you
20 can start the two minute timer and you can start
21 voting. Thirty seconds left. Okay. Looks like all

1 the votes are in. At this time, the two minutes are
2 up. And I want to say that we had one additional
3 voting member join us now, so we do have 12 voting
4 members for this particular vote at this time. We have
5 a unanimous vote, 12 out of 12. And I will read the
6 votes for the record. Dr. Cohn, yes. Dr. Berger, yes.
7 Dr. Shane, yes. Dr. Chatterjee, yes. Dr. Monto, yes.
8 Dr. Kim, yes. Dr. Badzik, yes. Dr. El Sahly, yes.
9 Dr. Bernstein, yes. Dr. James, yes. Dr. Portnoy, yes,
10 and Dr. Offit, yes. That concludes my reading of this
11 vote, and I will pass this now to Dr. El Sahly.

12 **DR. HANA EL SAHLY:** Question four: For the
13 quadrivalent 2022-2023 influenza vaccine in the U.S.,
14 does the committee recommend inclusion of a
15 B/Phuket/3073/2013-like virus for the Yamagata lineage
16 as the 2nd influenza B strain in the vaccine? Yes, no,
17 or abstain.

18 **MS. CHRISTINA VERT:** At this time, you may
19 start voting and the timer has started for two minutes.
20 You have 30 more seconds for the vote. It looks like
21 all the votes are in, so we will close the vote. We

1 have a unanimous vote, 12 out of 12 voting yes. And I
2 will read the specific votes for the record. Dr. Cohn,
3 yes. Dr. Berger, yes. Dr. Shane, yes. Dr.
4 Chatterjee, yes. Dr. Monto, yes. Dr. Kim, yes. Dr.
5 Badzik, yes. Dr. El Sahly, yes. Dr. Bernstein, yes.
6 Dr. James, yes. Dr. Portnoy, yes. And Dr. Offit, yes.
7 That concludes my reading of the votes and the voting
8 portion for today's meeting. I will now hand the
9 meeting back over to Dr. El Sahly.

10 **DR. HANA EL SAHLY:** Thank you, Christina. Do
11 you mind putting the names of the voting members on the
12 screen again? So now we will go the round table,
13 virtual round table to ask the members for their
14 rationale of their vote. I will begin with myself.
15 Dr. Wentworth presented data pertaining to the risk of
16 the virus, the H1N1, the H3N2. That is convincing that
17 those two strains might circulate and remain among
18 this population, the six (audio skip) stage should the
19 5A.1 rear its head would they be (audio skip) or not.
20 The treatment approach of course is important, but also
21 giving them their first two doses because partial

1 immunity is expected to prevent some severe outcomes,
2 at least in a fraction. Should that be the case, so
3 this was my rationale for voting yes. Dr. Monto?
4 Cannot hear you.

5 **DR. ARNOLD MONTO:** Yep. I think that this is
6 the best of the possible outcomes right now. We have a
7 good, not a great, vaccine. And we try to make it
8 better by being very careful in strain selection. I
9 join some of my colleagues in wondering about the
10 replacement of the B/Yamagata with another H3N2 to
11 hedge our bets, among other things. And to get us
12 higher titers as Dr. Wentworth mentioned. So I think
13 we go with the experts who have spent a long time
14 working on this and we can't do any better. Thank you.

15 **DR. HANA EL SAHLY:** Thank you, Dr. Monto. Dr.
16 Berger.

17 **DR. ADAM BERGER:** Thanks very much for a well-
18 run meeting, by the way. And just want to say, I agree
19 with everything you both said already. I think the
20 evidence around the strains are currently prevalent.
21 They're expected to be here in the U.S. in this next

1 flu season, plus the reactivity rates for each one of
2 the vaccines that were being, or for each of the
3 viruses and the ability to (inaudible) against that
4 suggest that these are really the best strains we ought
5 to put in. I do also reflect the same question around
6 the B/Yamagata lineage and whether it's necessary at
7 this point. But I think without further understanding
8 if it really is (inaudible) or if it's not, it's
9 probably the best idea to include it still at this
10 point. Something for the committee to take up at a
11 later date though.

12 **DR. HANA EL SAHLY:** Thank you, Dr. Berger.
13 Dr. Cohn. You are muted.

14 **DR. AMANDA COHN:** Can you hear me? Sorry.
15 First of all, I apologize for missing part of the
16 meeting, I had an unexpected issue. But I don't have
17 anything more to add than the prior members. I think
18 that in the current setting, this remains the best
19 choice, at least for this year. And I know that my CDC
20 colleagues will continue to watch this very closely.

21 **DR. HANA EL SAHLY:** Thank you. Dr. Shane.

1 **DR. ANDREA SHANE:** Thank you very much for the
2 really helpful and very informative presentations. I
3 agree with everything that has been said before. I
4 think we've had a blessing and a curse in not having a
5 very robust influenza season and based on the
6 information that we have, this helped to inform my
7 decision. I also would love to have as much
8 information as we can on the younger population because
9 this is one of interest, and I think one that often has
10 the most severe consequences from influenza infection,
11 so thank you very much.

12 **DR. HANA EL SAHLY:** Thank you, Dr. Shane. Dr.
13 Chatterjee.

14 **DR. ARCHANA CHATTERJEE:** Yes, my vote was
15 based on the data presented by colleagues from the CDC
16 and the DoD. As some of the members of the committee
17 have already said, these are the best data we have
18 based upon which to make our decision today. And, so,
19 I voted based on that information. Thank you.

20 **DR. HANA EL SAHLY:** Thank you, Dr. Chatterjee.
21 Dr. Kim?

1 **DR. DAVID KIM:** Oh, thank you so much,
2 everyone, who made the time and the effort to make the
3 presentations today. And I don't have much to add,
4 other than what's been said already, other than this
5 actually would make our recommendation for, when people
6 ask health care providers whether they should get the
7 quadrivalent versus trivalent vaccine. Because of all
8 that's been said about the B/Yamagata version.

9 And, actually, given the discussion we had
10 with some nuances on the composition of the flu
11 vaccine, it really does call for, so that we all can be
12 in a more comfortable place when making these decisions
13 of the need and the urgency to develop a universal
14 vaccine. So, with that, I just want to say thanks to
15 our colleagues who presented all the information and
16 also, that our recommendation is consistent with the
17 WHO recommendation and that they mutually validate one
18 another. So, thanks to all those people who made
19 tireless work to make these decisions as easy as
20 possible.

21 **DR. HANA EL SAHLY:** Thank you, Dr. Kim. Dr.

1 Bernstein?

2 **DR. HENRY BERNSTEIN:** I appreciate the
3 comments that everyone made and agree with what the
4 U.S. and the global surveillance data suggests, and I
5 was satisfied with Dr. Wentworth's incredibly detailed
6 presentation and explanation regarding whether or not
7 to consider changing the H1N1 strain, because I do
8 worry about those younger pediatric patients. And I
9 think that all the wonderful work that's done by the
10 CDC and others will keep us informed if changes need to
11 be made. Thanks to everyone.

12 **DR. HANA EL SAHLY:** Dr. Janes?

13 **DR. HOLLY JANES:** Thank you, nothing much to
14 add. I agree with all the statements that have been
15 made previously and I want to thank the speakers for
16 really incredibly thoughtful presentation. These
17 presentations seem to get more complex each year, but
18 even more nuanced and I really appreciated the work
19 that went into helping us think through the difficult
20 choices that need to be made, and the need for making a
21 decision now in order to make the production and

1 distribution timeline. I do want to second my
2 suggestion from earlier to perhaps consider revisiting
3 the data from a given year when we look at the data for
4 next year to see how well the final VE estimates map
5 alongside the immunology and the phylogenetic data that
6 we've been presented. But thank you very much.

7 **DR. HANA EL SAHLY:** Thank you, Dr. Janes. Dr.
8 Portnoy?

9 **DR. JAY PORTNOY:** Yeah, again, I'd like to
10 thank the speakers for their presentations. I'm really
11 impressed by the surveillance system, it's really
12 detailed and pretty amazing. I continue to be
13 concerned about the fact that what we're basically
14 doing is a guessing game. We're playing a game of
15 whack-a-mole where we develop the vaccine, whatever
16 vaccine we develop will put pressure on the virus to
17 mutate into something else, so we're never going to be
18 able to catch up with it.

19 And it's something that we have to take into
20 consideration. I would strongly urge that the industry
21 that produces the vaccines consider ways of either

1 increasing the number of strains that can be included
2 or using technology such as mRNA to increase the titers
3 so that you have a broader effectiveness of the
4 vaccines. Because until we do that we're really just
5 kind of chasing our tails. Virus will always find a
6 way. But this is the best we can do right now and I'm
7 happy with it. Thank you.

8 **DR. HANA EL SAHLY:** An interesting hypothesis
9 to test. Dr. Offit?

10 **DR. PAUL OFFIT:** Yes, I'd like to thank our
11 speakers for making a very difficult subject much
12 easier to understand. I mean, this is one elusive
13 virus. I trained in a flu lab in the early 1980s at
14 The Wistar Institute, in Walter Gerhard's lab, and he
15 was using monoclonal antibodies to define structure
16 functional relationships with the virus, and he was
17 working on a universal flu vaccine, I mean, he used
18 matrix protein to try and make a universal flu vaccine.
19 This was 40 years ago, I mean, it tells you how hard it
20 is to do that. And I suspect Dr. Portnoy eludes to
21 that we're probably going to be dealing with this on a

1 yearly basis for a while. But thanks, and again,
2 thanks to the speakers.

3 **DR. HANA EL SAHLY:** Thank you. And last, but
4 not least, Dr. Badzik.

5 **DR. DOUGLAS BADZIK:** First off, I wanted to
6 just thank everybody for the opportunity to participate
7 in this whole entire discussion. And for the
8 presentations. I thought that they were incredibly
9 well-presented in breaking down some very complex
10 subjects into a way that was very understandable. My
11 reason for voting was I just saw no compelling reason
12 to go and deviate from what the World Health
13 Organization had recommended. In particular in the
14 season when we did have a kind of limited ability to
15 have samples and surveillance compared to previous
16 seasons.

17 I think, particularly, the discussion that I
18 found incredibly useful was the discussion surrounding
19 H1N1 and kind of the discussion with regards to the
20 younger populations, and I think that will be something
21 that will be very important for us to follow through

1 this upcoming flu season, is to ascertain was that the
2 right decision, which it seems like it is. But, once
3 again, thanks everybody, and that's all I have.

4 **DR. HANA EL SAHLY:** I think we heard from all
5 of our members regarding the rationale of their vote.
6 And, with that, I turn the meeting over to Dr. Atreya.

7 **DR. PRABHAKARA ATREYA:** Thank you, Dr. El
8 Sahly, thank you all the members and the speakers. And
9 then, with that, I think the meeting is formally
10 adjourned now, 2:29. Thank you so much and have a good
11 afternoon. Bye-bye.

12 **DR. HANA EL SAHLY:** Bye.

13

14 **[MEETING ADJOURNED FOR THE DAY]**