UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCT ADVISORY COMMITTEE

MEETING

FRIDAY, FEBRUARY 17, 2006

The meeting was held in Conference Rooms A&B and C, Building 29B of the NIH campus, 8800 Rockville Pike, Bethesda, MD, at 1:00 p.m., Ruth A. Karron, Acting Chair, presiding.

PRESENT:

CHRISTINE WALSH, R.N.	EXECUTIVE SECRETARY
RUTH A. KARRON, M.D.	ACTING CHAIR
MONICA M. FARLEY, M.D.	VOTING MEMBER (via teleconference)
PHILIP LARUSSA, M.D.	VOTING MEMBER (via teleconference)
STEVEN SELF, Ph.D.	VOTING MEMBER (via teleconference)
BONNIE WORD, M.D.	VOTING MEMBER (via teleconference)
JOHN MODLIN, M.D.	VOTING MEMBER (via teleconference)
WALTER ROYAL III, M.D.	VOTING MEMBER (via teleconference)
CINDY LYN PROVINCE, RN, MSN, MA	CONSUMER REPRESENTATIVE (via teleconference
SETH HETHERINGTON, M.D.	INDUSTRY REPRESENTATIVE (via teleconference)

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PRESENT: (continued)

ROBERT COUCH, M.D.	TEMPORARY VOTING MEMBER (via teleconference)
THEODORE EICKHOFF, M.D.	TEMPORARY VOTING MEMBER (via teleconference)
BRUCE GELLIN, M.D., MPH	TEMPORARY VOTING MEMBER (via teleconference)
WAYNE HACHEY, D.O., MPH	TEMPORARY VOTING MEMBER (via teleconference)
PAMELA McINNES, DDS, MSC	TEMPORARY VOTING MEMBER (via teleconference)
MELINDA WHARTON, M.D., MPH	TEMPORARY VOTING MEMBER (via teleconference)
NORMAN BAYLOR, PhD	FDA
KAREN MIDTHUN, M.D.	CBER/FDA

SPEAKERS:

NANCY COX, Ph.D.	Centers for Disease Control and Prevention (via teleconference)
JERRY WEIR, Ph.D.	CBER/OVRR
ZHIPING YE, M.D., PhD	CBER/OVRR/LPRVD
ALBERT THOMAS	sanofi pasteur (via teleconference)

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(1:08 p.m.)

MS. WALSH: Good afternoon. I am Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome you all to this Advisory Committee meeting. There is a speakerphone for public participation located here in Conference A&A of Building 29B on the NIH campus.

This afternoon's session will consist of presentations and committee discussions that are open to the public. Michele, can you please remove the "Listen only" so I can do roll call now. Thank you.

At this time I would like to introduce the Committee members and ask that you acknowledge by saying Present.

The Committee Acting Chair, Dr. Ruth A. Karron, Professor, Department of International Health, Johns Hopkins School of Hygiene and Public Health.

ACTING CHAIR KARRON: Present.

MS. WALSH: Dr. Monica M. Farley,

Professor of Medicine, Department of Medicine, Emory University School of Medicine.

DR. FARLEY: Present.

MS. WALSH: Dr. Philip S. LaRussa, Professor of Clinical Pediatrics, Columbia University.

DR. LaRUSSA: Present.

MS. WALSH: Our Consumer Representative, Cindy Lyn Province, R.N., M.S.N., Associate Director, Bioethics Center of St. Louis.

MS. PROVINCE: Present.

MS. WALSH: Dr. Steven Self, Professor, Department of Biostatistics, University of Washington.

DR. SELF: Present.

MS. WALSH: Dr. Walter Royal III, Associate Professor, Department of Neurology, University of Maryland School of Medicine.

DR. ROYAL: Present.

MS. WALSH: Our Industry Representative, Dr. Seth Hetherington, Chief Medical Officer and Vice President, Clinical Development, Inhibitex, Alpharetta, Georgia.

DR. HETHERINGTON: Present.

MS. WALSH: Dr. Bonnie M. Word, Assistant Professor of Pediatrics, Baylor College of Medicine, Texas Children's Hospital. Dr. Word, are you on the line?

Dr. John Modlin, Professor of Pediatrics, Dartmouth Hitchcock Medical Center. Dr. Modlin, are you on the line?

Now I would like to introduce our consultants and speakers for today's meeting.

Dr. Nancy Cox, Influenza Branch, Centers for Disease Control and Prevention.

DR. COX: Present.

MS. WALSH: Dr. Theodore Eickhoff, Professor of Medicine, Division of Infectious Diseases, University of Colorado, Health Science Center.

DR. EICKHOFF: Present.

MS. WALSH: Dr. Bruce Gellin, Director, National Vaccines Program Office, Department of Health and Human Services.

DR. GELLIN: Present.

MS. WALSH: Lieutenant Colonel Wayne

Hachey, Director of Deployment Medicine and Surveillance Force, Health Protection and Readiness, Office of the Assistant Secretary of Defense for Health Affairs.

LT. COL. HACHEY: Present.

MS. WALSH: Dr. Pamela McInnes, Director, Center for Integrative Biology and Infectious Diseases, National Institutes of Dental and Cranial Facial Research, National Institutes of Health. Dr. McInnes did tell me that she may be a little bit late in dialing in today.

Dr. Melinda Wharton, Acting Deputy Director of the National Immunization Program, Center for Disease Control and Prevention.

DR. WHARTON: Present.

MS. WALSH: Dr. Robert Couch, Professor of Medicine, Microbiology and Immunology, Department of Microbiology, Baylor College of Medicine.

DR. COUCH: Present.

MS. WALSH: Michele, if you can put the lines back on silence mode, that would be terrific, if you could; and could you please tell me when Dr.

Bonnie Word and Dr. John Modlin join us?

DR. COUCH: Dr. Bonnie Word, I told the operator, is here with Robert Couch. We are at the same site. She is here.

DR. MODLIN: And this is John Modlin. I have just joined.

MS. WALSH: Okay. Thank you.

Now I would like to introduce the Influenza Vaccine Manufacturer that will be participating and speaking at this teleconference: Albert Thomas, Director of Viral Manufacturing, Sanofi Pasteur.

MR. THOMAS: Present.

MS. WALSH: I would like to thank all Committee members, consultants and manufacturers for taking the time to join us today. I also wish to thank Dr. Karron for agreeing to step into the Acting Chair role for today's meeting.

Now I would like to introduce some CBER staff members that will be participating in today's meeting and are currently seated in this room.

Dr. Karen Midthun, Deputy Director for

Medicine, CBER; Dr. Jerry P. Weir, Director, Division of Viral Products, OVRR; Dr. Zhiping Ye, Research Microbiologist, Laboratory Pediatrics and Respiratory Viral Diseases, Division of Viral Products, OVRR; and Dr. Norman Baylor will be joining us today also, Director, Office of Vaccines Research and Review.

I would like to thank Denise Royster, Committee Management Specialist, VRBPAC Advisory Committee.

I would ask that all Committee members speak slowly and clearly each time you speak. We do have a transcriber present who will need your assistance in order to accurately transcribe all comments to the appropriate Committee member.

I would now like to read into the public record the conflict of interest statement for this meeting.

The Food and Drug Administration is convening today's meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the Industry

Representative, all members and consultants of the Committee are Special Government Employees, SGEs, or regular Federal employees from other agencies, and are subject to the Federal conflict of interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with Federal ethics and conflict of interest laws, including but not limited to 18 USC 208 and 21 USC 355(n)(4), is being provided to today's participants in today's meeting and to the public.

FDA has determined that members of this Advisory Committee and consultants of the Committee are in compliance with Federal ethics and conflict of interest laws, including but not limited to 18 USC 208 and 21 USC 355(n)(4).

Under 18 USC 208 applicable to all government agencies and 21 USC 355(n)(4) applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special Government Employees who have financial conflicts when it is determined that the agency's need for a particular individual's services

outweighs his or her potential financial conflict of interest (Section 208) and where participation is necessary to afford essential expertise (Section 355).

Members and consultants of the Committee who are Special Government Employees at today's meeting, including Special Government Employees appointed as Temporary Voting Members, have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their employer, spouse or minor child, related to discussions on the strain selection for the influenza virus vaccine for the 2006-2007 season.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, writing, patents and royalties and primary employment.

For today's agenda, the Committee will review and discuss the strain selection for the influenza virus vaccine for the 2006-2007 season. In accordance with 18 USC Section 208(b)(3), waivers have

been granted to Dr. Robert Couch, Dr. John Modlin, and Dr. Ruth Karron. A copy of the written waiver may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 18A30 of the Parklawn Building.

Dr. Seth Hetherington is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Inhibitex, Inc. Inhibitex has licensed a technology to Wyeth for potential unrelated vaccine.

In addition, his spouse is employed by GlaxoSmithKline and has a financial interest in her employer. Industry representatives are not Special Government Employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members and consultants that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the

record. FDA encourages all other participants to advise the Committee of any financial relationship that you may have with the sponsor, its products and, if known, its direct competitors.

That ends the reading of the conflict of interest statement. Dr. Karron, I turn the meeting over to you.

ACTING CHAIR KARRON: Welcome, everyone, to the annual VRBPAC Influenza Strain Selection meeting. I would particularly like to welcome Dr. John Modlin, our newest VRBPAC member, and our guest speakers and consultants for today.

As you know, this is the first influenza strain selection meeting to be conducted by teleconference. After each presentation, you will be able to notify the operator if you have any questions or comments, and she will announce you. Please be patient if there are technical difficulties, and please do ask questions, since I think our discussions are an important part of this process.

I also know that all of us would like to hear from Dr. Cox about H5N1 influenza, and we have

provided time for a presentation and a brief discussion at the end of the meeting after the strain selection process is completed.

Our first speaker for today is Dr. Jerry Weir from the FDA. Dr. Weir.

DR. WEIR: Thank you. I will be reading and presenting from my slides that Christine Walsh has sent out to all of the members.

To get started, first of all, thank you all for being here, for being on the phone. I am Jerry Weir, the Director of the Division of Viral Products, and I am going to provide the introduction today to the Vaccines and Related Biological Products Advisory Committee.

As you know, we are here to discuss the influenza virus vaccine composition for the year 2006-2007. Go to the slide 2.

Specifically, we are here to obtain the VRBPAC committee recommendation regarding the selection of influenza A, H1N1 and H3N2 and B virus for the 2007-2006 influenza vaccines for use in the United States. Slide 3.

The reason that we change strains of influenza vaccines is to ensure vaccine efficacy. Basically, vaccine efficacy relates to vaccine potency and directly to immunogenicity, as well as to the match of the vaccine hemagglutinin neuraminidase with wild type viruses.

As everyone knows, antigenic drift of HA and NA is continuous in influenza A and B viruses. In fact, the first evidence that there was evidence of reduced vaccine effectiveness because of antigenic drift occurred within two years after influenza vaccines were first licensed in the United States. Next slide.

Each year when we get together for this annual strain selection committee, we ask ourselves four questions. These are shown on the next slide.

First of all, are new drifted or shifted influenza viruses present? Second, are these new viruses spreading in people? Third, do current vaccines induce antibodies against the new viruses, particularly and specifically glutenin? Finally, are strains suitable for vaccines available? This is

essentially what we will be asking ourselves today. Next slide.

To remind everyone, the strains of virus that are in the current vaccine, the 2005-2006 virus, are listed on this slide. Vaccines contain an A/New Caledonia 20/99(H1N1)-like virus, an A/California 7/2004(H3N2)-like virus. This was changed from the previous 2004-2005 season, and specifically in the vaccine is an A/New York 55/2004 virus, and the B strain B-Shanghai/361/2002-like virus -- this is of a B/Yamagata/16/88 lineage -- and two viruses specifically were in the vaccines, a B/Jilin/20/2003 in the live attenuated virus and a B/Jiangsu/10/2003 in the trivalent inactivated vaccine. Next slide.

Also, as you know, we now have four licensed manufacturers in the United States, three inactivated influenza vaccines, Sanofi Pasteur, Chiron, GSK, and one live attenuated vaccine manufacturer, Medimmune. Next slide.

This slide and the one that will follow show the approximate timelines for vaccine production. Now part of the reason that we are here today is

because these timelines for influenza vaccine production are tight and relatively inflexible.

If you look at this slide, you see some of the activities that go on during the year and the times during the year at which they take place. Surveillance, of course, takes place throughout the year in both hemispheres, as well as work on new reference strains and reagents.

Two times a year, recommendations are made for the composition of the vaccines. This time of the year in February and sometimes as late as March, recommendations are made for the strains to be used in the northern hemisphere for the next year, and that is why we are here today.

In the fall of each year, usually around September, recommendations are made for the composition of strains to be included in the southern hemisphere vaccine. Also, you see preparation of new seed viruses takes place throughout the year, and monovalent production begins in January and sometimes continues as late as November of the same year. Trivalent formulation follows this, hopefully, and

usually beginning as early as late May/June for distribution of vaccine, hopefully, starting in July, and vaccine usage beginning in September. As I said, this is a very tight time schedule that we all have to deal with.

The next slide, in fact, shows an example of how long it actually takes to incorporate a new strain into the vaccine from the time that it is identified at a meeting such as we are in today. There's actually some blue and some black on this slide.

The blue represents a new strain change, and you can see, without spending too much time on it, by the time we go through the process of obtaining references viruses, reference reagents, seed virus preparation, staggered production of the three monovalents, release formulation, filling, it can take 20 to 24 weeks before a vaccine can actually be distributed.

So again, essentially the sooner we can make recommendations, the sooner we can move forward with vaccine production. Next slide.

Earlier this week there was a WHO consultation on the composition of vaccines to be used for the northern hemisphere 2006-2007. This occurred on Monday and Tuesday of this week, February 13-14, and on Wednesday, February 15, these results were announced to the public.

At this meeting, the WHO discussed the antigenic and genetic characterization of influenza viruses that had been investigated in the WHO collaborating centers for reference and research on influenza.

The WHO also reviewed the serological studies with inactivated influenza vaccine and, as I said, on Wednesday issued recommendations for vaccine composition for 2006-2007 northern hemisphere. This information is available on their website, which is listed in this slide, and I think Christine Walsh also sent that to the VRBPAC member separately. Next slide.

A list of WHO recommendations that were made earlier this week: It is recommended that vaccines to be used in the 2006-2007 northern

hemisphere winter contain the following: An A/New Caledonia 20/99(H1N1)-like virus; an A/Wisconsin 67/2005(H3N2)-like virus -- this is a new strain recommendation by the WHO; and finally, a B/Malaysia 2506/2004-like virus. This is a new strain recommendation for the northern hemisphere, but it is the same strain that was recommended this past September for use in the southern hemisphere. Next slide.

Now as always, it is the responsibility of each national regulatory authority to approve the specific vaccines used in each country. So today we will review the surveillance data, both the epidemiology and the antigenic characteristics of recent virus isolates. Dr. Nancy Cox from the CDC will be presenting that information in the following talk.

We will also review serological responses to current vaccines. Dr. Zhiping Ye from CBER, the Food and Drug Administration, will review that data, and Dr. Ye will also present information concerning the availability of candidate strains and reagents.

We will also hear from the manufacturers in a brief presentation.

Then we will ask the Committee to discuss which strains should be recommended for the antigenic composition of the 2006-2007 influenza virus vaccine.

Now I will stop here. There are two more slides on my presentation, but I will come back to those before the Committee begins deliberations and discussion. I will turn it back over to Dr. Karron.

ACTING CHAIR KARRON: Thank you, Dr. Weir. Are there questions for Dr. Weir?

MS. WALSH: Excuse me, Michele. Can you turn everyone on -- remove the silent?

I think at this time we will move on to our next speaker, Dr. Nancy Cox from the CDC. Dr. Cox.

DR. COX: Yes.

MS. WALSH: Excuse me. Dr. Cox, before you start, this is Christine. I will be running your slide show from the projector that I have in the room here. So if you could just say "next slide," and for all the members, that would be very helpful.

DR. COX: Okay. Thank you very much.

I would like to have everyone turn to page 2, the second slide where we have acknowledged all the people from CDC who have contributed to the information that we are presenting here today. Next slide, please.

First, I am going to briefly review U.S. surveillance data. I would like to preface my specific remarks with a comment that we have had a relatively mild and moderate influenza season. Of course, it varies state by state and region by region, but as I go through the slides you will see how relatively mild this season has been compared to the last two influenza seasons.

So on page 4, or slide 4, you will see that we have had predominantly influenza A viruses reported to us through the WHO and the NREVSS Collaborating Laboratories. Of the influenza A viruses that have been subtyped, the majority are influenza A(H3N2).

I will just make a comment here that, while not all of the H1N1 viruses that have been

identified, or all the H1 viruses that have been identified have had their neuraminidases subtyped. All that have, both from the United States and from abroad, have been H1N1 viruses, and this is true for all of the four collaborating centers. So it may be that H1N2 viruses have ceased to circulate.

We have, in addition, had relatively small numbers of influenza B viruses reported in the United States. The black line that you see represents the percent positive of the total number of respiratory virus specimens that are sent in to the states for analysis or are isolated by the state health departments.

You can see that we haven't really reached 15 percent positive; whereas, in some years we have reached a percent positivity of between 20 and 30 percent. Next slide, please.

The next slide shows that the sentinel physicians who have reported to us -- and we have approximately 1,000 sentinel physicians who report on a weekly basis; we have about 2,000 enrolled, and of those 2,000 about half report each week. You can see

the red line in the graph, which shows the relative influenza activity this year compared to the activity the previous two years.

Of course, you will remember that during the 2003-2004 season we had a very early season, and then last year we had a relatively late season. This year, we saw a small peak of influenza-like illness reported by the sentinel providers in week 52 with a subsequent overall national decline in activity and a little bit of an increase again in week four.

We are still not very far above the baseline which at this time of year is just slightly above two percent. Next slide, please.

This slide on page 6 shows the pneumonia and influenza mortality for the 122 U.S. cities. This shows cumulative data up to the week ending the 4th of February, and the most recent data are consistent with mortality being below the baseline.

So we really haven't seen any excess deaths attributed to pneumonia and influenza this year, in contrast to the previous years and, certainly, in contrast to the 2003-2004 season where

we saw a very substantial peak of excess deaths. Next slide, please.

We have added some new components to our surveillance system, as you probably know if you have been reading our weekly reports on the web; and slide 7 shows the laboratory confirmed cumulative hospitalization rates for children aged zero to four and, separately, five to 17 years of age for the 2005-2006 season in red, for the 2003-2004 severe season in blue, and for the 2004-2005 season in green.

What you can tell very clearly is that the current season is less severe in terms of hospitalization of children in both age groups and, of course, in 2003-2004 we had substantial hospitalization and mortality in young children. Next slide, please.

We also have a second system which looks at laboratory confirmed cumulative hospitalization rates, this time just for children zero to four years of age. This is a very intensive surveillance network, much more limited than the previous one, and it is an active surveillance where all the children

are swabbed, and PCR is used to try to determine the cause of respiratory illness.

Once again, you will see the current season shown in red, and it is -- the hospitalization is lower than in previous years. You will once again note that in blue you see the very substantial hospitalization of children less than four years of age during the 2003-2004 season. Next slide, please.

This slide shows the level of activity in the United States in each state, and in contrast to some years where we have seen almost the entire map turn red at some point in the season, this year we have seen activity starting primarily in the west and southwestern part of the United States. Now we are seeing widespread activity on the east coast, a good bit of regional activity in the southeast, in the midwest and on the west coast as well.

In addition, there is some local activity in certain states, but again this has been a relatively mild season when we look state by state. Next slide, please.

I will be talking about influenza A(H1)

viruses. First, and on the slide on page 11 you will encounter the first hemagglutination inhibition table, and I will walk you through this fairly slowly and carefully, for those of you who are less accustomed to looking at hemagglutination inhibition data.

In the top part of the chart we have our reference antigens, and going from reference antigen 1 through 6, we have developed post-infection ferret serum for each of these reference antigens, and we do a hemagglutination inhibition test where we look for the homologous titers -- that is the titer of hemagglutinating antibody -- hemagglutination inhibition antibody that you see for each of the reference antigens diagonally in red and underlined across the top part of the chart.

You will note that, for different antigens, you get different homologous titers, and that is because some HAs are intrinsically more immunogenic than others, and you will note that we have highlighted the second column, which is the column that represents reactions between the New Caledonia antiserum and all of the reference antigens

and the test antigens.

Now what we are looking for in terms of antigenic variation is a reduction in titer of fourfold or greater compared to the homologous titer for that reference virus. So for the New Caledonia virus, which is the reference virus which has been in the vaccine for a number of years, we see we have a homologous titer of 1280, and you can see that even within our reference antigen panel, we have two antigens, the Hawaii/15 and the Jiangxi/160, which have titers of 40, which is certainly a significant reduction.

We have over the course of time since the New Caledonia strain was chosen to be a vaccine strain seen occasional isolates with reductions in titer as compared with a homologous titer. But there has been no distinct pattern, and the proportion of viruses that have reduced titers has remained low over time.

Now if you look at the test antigens, you will see the first two test antigens are viruses from the United States, one from Arizona and one from Pennsylvania. The remainder of the viruses on that

particular table are from Asia. All of the isolates that are shown in this particular test have collection dates between the middle of October and early January. So they are relatively recent viruses.

The reason that the majority of the viruses in this table are from Asia is that Asia has had more H1N1 activity to date than other parts of the world, and many of the most recent viruses are from Asia. So we have put this data before you today.

Now you notice that the majority of the viruses shown on this table are well inhibited by antiserum to the New Caledonia, but you will see that there are some viruses at the bottom of the table which are less well inhibited by antiserum to the New Caledonia virus, and there is one at the very bottom which is from Korea, the Daejeion virus, which has a titer of only 40 against the New Caledonia serum, but a titer of 320 against the Jiangxi/160 serum. But it is relatively rare to see viruses that have low titers within the New Caledonia that actually have higher titers with any of the newer sera that we have developed and, of course, we have simplified our

table.

We have put many more viruses into ferrets than you can see here, and I will make some additional comments about differentiating viruses when I get to the evolutionary tree. But now I would like to move on to the next slide, please, Slide 12, where we have our frequency table showing for the period April 2005 to September 2006 -- sorry, April 2005 to September 2005, that all of the viruses that we tested from North America, Europe, Asia, Central and South America, Australia, New Zealand and Africa were New Caledonia-like.

We have had a few, as I mentioned, lower reacting viruses during the most recent period, October 2005 to January 2006. So that now we have a total of only 12 or 16 percent out of the total of 77 viruses isolated during this period that have reductions in titer. We should go to the next slide, please.

Here on this slide you are looking at the evolutionary relationships among the HA genes of the H1 viruses. I hope you are looking at this in color.

You will see the vaccine strain, New Caledonia, in red. In blue you will see a number of the egg isolates that we have obtained through the egg CRADA, and you can see that we have really quite a large number of egg isolates.

Then you will also notice that we have shown amantadine resistant and amantadine sensitive viruses by symbols. There is a circle with an "R," indicating that the virus has been tested and is resistant to amantadine, and amantadine sensitive where you have green squares and an "S" in the middle, and that indicates that the virus has been tested and is sensitive. For the viruses with no symbols behind them, we haven't yet tested the viruses.

What you will notice about the evolutionary tree is that the virus -- the HAs of the H1 viruses that are circulating are falling into two distinct sub-lineages, not nearly as distinct as the D sub-lineages, but you can see that there are a number of amino acid changes between viruses in the upper and lower parts of the dendrogram. However, I would like to emphasize that, in spite of the fact

that we do see some low reactors in both the upper and the lower parts of the dendrogram, and those low reactors are indicated by LR, and by low reactor I mean a virus that has an HAI antibody titer that is reduced by fourfold or greater compared to the homologous titer for the New Caledonia vaccine strain.

We have low reactors in both parts of the dendrogram and, furthermore, we cannot or have not yet been able to antigenically distinguish viruses in the upper and lower parts of the dendrogram. So you will see both viruses that are inhibited very well by the New Caledonia antiserum in the upper and the lower parts of the dendrogram, and viruses that are less well inhibited in both the upper and lower parts of the dendrogram.

It does appear to us when we have done a timed series looking at where the most recent viruses are that they are tending to cluster in the lower part of the dendrogram, although you will indeed see viruses that were isolated during 2005 in the upper portion of the dendrogram. Next slide, please.

Likewise, the neuraminidase genes of

currently circulating viruses actually separate less clearly, but still you can see that there are two groups, and they share different amino acid changes. The egg isolates -- Once again, we have fewer data for neuraminidase, because we don't sequence as many neuraminidase genes as we do HA genes, but we do try to keep up with the primary reference viruses and some key egg isolates which might possibly, if needed, become vaccine candidates.

You will see that there are two groups, one represented by Shenzhen/141 at the bottom and another represented by Kentucky/1 at the top, and those neuraminidases tend to segregate with the HAs, as I said before.

I am going to skip over slide 15, because the serology data will be discussed by Dr. Zhiping Ye later on.

Ruth, would you like me to stop here and ask for questions or shall I go through my presentation and take all questions at the end?

ACTING CHAIR KARRON: Why don't you go through the whole presentation, Nancy, and then we

will take questions at the end.

DR. COX: Okay, that sounds good.

Moving right along to the H3N2 viruses, if you will look at Slide 17, you will see that there is an HI table that looks fairly complex, because we have different color coding, and we have some additional information at the top right under where it says "reference ferret antisera."

You can see that there is a blue line over the antigens Hong Kong/2831, Anhui/1239 and Hiroshima/52 and Wisconsin/67. In that blue bar it says: 193F plus 225N. These are two amino acid changes that are signature changes for the majority of the viruses that we are seeing now.

The first column is the column for the vaccine strain, the recommended vaccine strain California/704. We made a recommendation that the vaccine strain be California/704-like.

In the second column you will see the actual vaccine reassortant that was used, and this is the New York/5504 PRA reassortant X-157. So what we can see is that we have a homologous titer of 640, and

there are a number of viruses that have titers of 160, which is a fourfold reduction compared to the homologous California/7 titer.

Likewise, if we look at the homologous titer for the New York reassortant virus, we see that it is 1280 and that there are really quite a number of viruses that have a four- to eightfold reduction in titer as compared to the homologous New York/55 titer.

I would like to point out that the Wisconsin/67 virus on the far right has a homologous titer of 1280 with its antiserum, and that -- and to just point out that it does a relatively better job at covering the currently circulating strains than either the California serum or the New York serum. You can see that we have higher titers along the righthand side of the table than we do on the lefthand side.

Represented here, please note that we have a number of viruses from the United States. We have a couple from Mexico. We actually had quite a number of viruses from Mexico that we were able to analyze before the vaccine strain selection meeting from the

National Influenza Center in Mexico, and that was indeed very good.

The rest of the viruses are all from Asia except for the last one, which is from Italy. You will notice that the viruses, antigens Number 24, 25, and 26, are all from Mongolia, and all of those viruses have somewhat reduced titers to the California and New York antisera. And I would just like to point out that these are relatively recent viruses with some of them being fairly recent, I guess. Most of them are from December.

On Slide 18 we have a frequency table which shows that, during our summer season, the winter season and the summer at southern hemisphere from April 2005 to September 2005, that we were seeing approximately 27 -- sorry, 20 percent of 346 viruses characterized that had a fourfold or greater reduction in titer to both the California and the New York/55 reference strains; and we have used fairly strict criteria here. We had to have reductions to both the California and the New York antisera.

We noted that there had been an increase

this year in the proportion of viruses with reductions in titer, though for the period between October 2005 and the current time we have seen 28 percent of 200 viruses that were characterized with reductions in titer that were fourfold or greater.

If we could move on to slide 19, please: Here we are looking at what I referred to before in terms of the coding at the top of the HI table. This is a dendrogram showing the evolutionary relationships among the HA genes of H3 viruses.

Once again, you will note that all of the HAs representing the viruses listed in blue have egg isolates. So we have a large number of egg isolates this year, thanks to the egg CRADA, and we also have focused a lot of attention on determining whether the currently circulating strains were resistant to amantadine and rimantadine.

You will see that on this particular slide the amantadine resistant viruses are designated by the blue triangles, while the sensitive viruses are designated by the green triangles.

You will see that the majority of the

viruses are in that top group -- the majority of the current viruses, the 2005 viruses, that we have been seeing in the United States and around the world are in that top group which share the serine, the phenylalanine change at 193 and the aspartic acid to asparagine change at 225; and we noted this group of viruses first emerged in Asia, particularly in China and Hong Kong, and now this group of -- this genetic group of viruses is predominating worldwide and, of course, the majority of these viruses are resistant to amantadine and rimantadine.

If you would note that the vaccine strain, the current vaccine strain, A/California/7/2004, which is shown in red and with a box around it, is amantadine sensitive, and the majority of the viruses last year were rimantadine and amantadine sensitive. Next slide, please.

Here you will see the evolutionary relationships among the N2 neuraminidase genes. There is not so much variation among the neuraminidase genes of currently circulating viruses.

The majority of recent strains have been

in that top group where you see Wisconsin/67, our reference strain, Hiroshima/52, another reference strain, and all of these current viruses share the aspartic to asparagine change at amino acid 93 in the neuraminidase.

I don't have very much more to say about the neuraminidases. They just haven't changed very dramatically. Next slide, please. We will skip the serology, because I believe Zhiping will be covering that. So we will move on to the influenza B viruses and start with Slide 23.

This chart is a compilation of data which was provided by WHO Collaborating Centers in Atlanta, London, Melbourne and Tokyo. So we put all of our data together, and I would like to thank Sasha Klimov for putting this slide together while I was gone to Geneva.

We also took reports from the European Influenza Surveillance Scheme which are posted on their website and from the National Influenza Center in Canada which sends us weekly reports.

I just wanted to demonstrate here that

H3N2 viruses have predominated in reports worldwide, and they have constituted 45 percent of the influenza isolates that have been characterized between October 2005 and the current time.

H1N1 viruses have made up a smaller proportion, of course, but still there have been a number of isolates, and they constitute 19 percent of the total influenza viruses characterized. But I want now especially to focus on the influenza B viruses, because as you know from participating during the past few years, that we have two very distinct lineages of influenza B viruses circulating worldwide.

They are represented by the reference strains, Yamagata and Victoria, and we refer to these distinct antigenic and genetic lineages as the B/Yamagata and the B/Victoria lineages.

You will note that the B/Victoria lineages is predominating at the current time, and so 27 percent of the current influenza viruses are of the B/Victoria lineage, as opposed to 9 percent of the total influenza viruses being B/Yamagata lineage viruses; and it is actually about a third of the B

viruses being B/Yamagata, and about two/thirds are B/Victoria lineage viruses. Next slide, please.

I would like to thank my WHO colleague, Wenqing Zhang, for compiling the next graph which shows the number of influenza B viruses characterized and reported to Geneva headquarters monthly from September 2005 through January 2006.

In black you will see the B/Yamagata lineage viruses represented. In pink you will see the B/Victoria viruses represented, and you can see that in September Victoria viruses predominated. There was a switchover in October and November where Yamagata lineage viruses predominated by a small margin, very small margin when you look at the numbers worldwide, and now you see that, once again, the Victoria lineage is predominating.

Dr. Alan Hay, my colleague from the WHO Collaborating Center in London, mentioned that approximately 400 outbreaks in schools had been reported in the UK. There were influenza B outbreaks in the schools, and as far as the viruses had been characterized to date, they had been B/Victoria

viruses that were causing these outbreaks.

So if you go to the next slide on page 25, you will see an HI table of Type B influenza viruses, and you will note that you can very easily and very distinctly distinguish the Yamagata lineage viruses shown on the righthand side of the table and represented by Shanghai/361/2002 and B/Florida/7 reference strains. Those are highlighted in yellow.

On the righthand side of the table you will see four strains, starting with Shanghai/7, Hong Kong/310, Malaysia/2506/ and Ohio/1, which represent the B/Victoria lineage.

You will note that the titers of the Yamagata lineage viruses have become somewhat reduced to the Shanghai/361 reference virus which was recommended for inclusion. Shanghai, a 361/like virus, was recommended for inclusion in the previous Yamagata lineage vaccine strain.

The Florida/7 virus, which is an egg isolate, induces antibodies which actually cover the currently circulating B/Yamagata viruses very well.

On the righthand side you will see that

titers are reduced, especially to some of the viruses

in the lower part of the table, to the Shandong/7 and Hong Kong/310 reference ferret antisera, and you will see that, in our hands at least, antiserum to the Ohio/1 virus covers recently circulating influenza B viruses on the Victoria lineage shown in the green block. Here we have represented viruses from the U.S., from Asia and from the United Kingdom.

We will go on to the next slide, which shows data from the WHO Collaborating Center in Melbourne, Australia. They are seeing a similar pattern, only they switched their viruses around, and they have the B/Victoria viruses on the lefthand side of the table and the B/Yamagata lineage viruses on the righthand side of the table.

Just going to the B/Yamagata-like viruses, you will see that their Florida antiserum, like ours, covers the currently circulating Yamagata lineage viruses quite well, and that if you move to the lefthand side of the table and look at the Victoria lineage viruses, you will see that the Malaysia/2506 and Ohio/1/2005 antisera cover currently circulating B/Victoria lineage viruses quite well compared to the

Brisbane/32, which was their vaccine strain previously.

If you move on to the frequency table on Slide 27, you will see that the viruses that have circulated during the southern hemisphere winter season have been predominantly Victoria lineage or Hong Kong-like and low to Hong Kong, primarily low to Hong Kong/330, and a minority were on the Yamagata lineage.

The same holds true, even though there are relatively fewer viruses analyzed, actually many fewer viruses analyzed during the most recent period, October 2005 to December 2005. You will see the majority of the viruses are in the Victoria lineage and represented by Hong Kong/330, and they are low to Hong Kong; and of the viruses that were on the Yamagata lineage, most of them were like the B/Florida. Next slide, please.

Here we have demonstrated the evolutionary relationships among the HAs of the B/Yamagata lineage viruses. If we were to put the B/Yamagata and B/Victoria viruses on the same dendrogram, you would

see that they have really drifted very far apart.

The reference antigens are pointed out with the black stars. The egg isolates, once again, are shown in blue with a hash-mark behind. The vaccine strain is shown toward the bottom of the dendrogram in red and a box, Shanghai/361/2002. You can see that the viruses have moved on somewhat, but remember that the Yamagata lineage is in the minority.

The Florida virus is quite representative of the strains that are circulating at the current time. Next slide, please.

Now you are looking at the evolutionary relationships among influenza B viruses on the Victoria lineage. Again, we have the egg isolates shown in blue, and we have a large number of them.

We can see here that there are two genetically distinguishable groups, one at the bottom of the dendrogram represented by the Malaysia/2506/2004 which is the vaccine strain that was chosen for the southern hemisphere for next year, and a group at the top which is represented by the Ohio/1/2005 virus.

As you can recall from the previous HI tables, we have not been able to distinguish these viruses by antigenic means. So in spite of the fact that we have seen these genetic changes between the Ohio/1 and the Malaysia/2506, we have not been able to distinguish viruses in these two parts of the dendrogram using ferret -- post-infection ferret antisera.

The next slide shows the evolutionary relationships of the neuraminidase genes and, as you may recall, there was a reassortment event that occurred between viruses on the Yamagata and Victoria lineages sometime ago, and we have indicated the neuraminidases along the right with a bar that says SHD-SIC reassortants.

You will see that at the bottom of the dendrogram you have the Florida/7 neuraminidase represented, and that is a virus of the Yamagata lineage. Then you can see the Malaysia and Ohio virus neuraminidases represented by the majority of the neuraminidases in that region where we saw neuraminidases of the reassortant viruses.

Okay. If you would move on to the next slide, we will skip that, because that shows the serology in the pediatric populations, and I think Zhiping will be going through that data later. I will stop there, because the last part of my presentation concerns H5N1 viruses, and we will be covering those viruses at the very end of our discussions. Thank you.

ACTING CHAIR KARRON: Thank you, Nancy. We can get questions and, while we are waiting for some questions, I have one for you, Nancy, which is: I was wondering if you could contrast our situation with B/Victoria and B/Yamagata this year as compared with last year.

DR. COX: Yes. I think I would characterize it as being clearer in terms of directionality than last year. We have had -- At least for us in the United States, we have had relatively little B activity in the United States.

So I think that that indicates that we could have B activity next year; and because the majority of B activity in Asia and Europe is clearly

B/Victoria lineage activity, now which is either at the peak or somewhat late in the season, I think that we are much more likely to have B/Victoria activity next year based on previous patterns.

I would say that with a caveat, that influenza viruses are inherently unpredictable, but just in terms of the patterns we have seen before, I would say that the directionality is a bit more clear to me than it has been sometimes in the past.

ACTING CHAIR KARRON: Thank you. Are there questions for Dr. Cox?

MS. WALSH: Excuse me, Michele. Is the silence mode off?

OPERATOR: No. Thank you. Once again, for the questions press *1, please. We do have a question from Philip LaRussa. Your line is open.

DR. LaRUSSA: Dr. Cox, you may have mentioned this, but is the percentage of A strains that were fully characterized the same or different than it is in previous years?

DR. COX: It is actually greater than in previous years.

DR. LaRUSSA: Thank you.

OPERATOR: Thank you. Robert Couch, your line is open.

DR. COUCH: I have two questions, Nancy. You can answer both of them. One is: Has H1N1 been the dominant virus in any of the outbreaks or any of the populations from which you have sampling from Asia? Do we have it as the dominant outbreak virus anywhere?

The second question is: In looking at the B dendrogram, you note that Christchurch is way out to the right and Wellington not far from it, and they had a sizeable B outbreak, is my recollection. Are their viruses still covered by the ferret serum fairly well?

DR. COX: Okay. Your first question, was H1N1 dominant in any countries? Yes. H1 was the dominant strain isolated in China, and I believe Taiwan, but they didn't have particularly severe outbreaks, of course.

Then let's see, let me flip back.

DR. COUCH: Christchurch.

DR. COX: Would be Christchurch. Their

viruses were -- Okay. Their viruses were actually well inhibited by their antiserum to Malaysia/2506.

DR. COUCH: Thank you.

OPERATOR: Next question, Monica Farley, your line is open.

DR. FARLEY: Thank you. Nancy, on page 27, the table of the influenza B isolates that have been characterized by CDC: At the bottom half, the more recent isolates, it looks -- Is it not showing that more of the isolates were actually Yamagata?

DR. COX: It is, for the U.S. So this is just -- So if you look -- The numbers are really small. I didn't go through the table very carefully. I sort of skipped over it. The numbers are very small, and the majority of them are from the U.S., but when you look globally, you see a very different pattern, as shown on --

DR. FARLEY: The top of the table?

DR. COX: Yes. Well, as shown on the table on page 23, Slide number 23, where when you look globally, you see that the numbers are much greater. You have 453 influenza B viruses, and about two-thirds

of them are B/Victoria, and also that the most recent isolates that haven't even been characterized yet from the school outbreaks, or hadn't been tested -- they had been -- it had been determined if they were Victoria or Yamagata lineage, but they hadn't been fully characterized using post-infection ferret sera, though they are B/Victoria-like.

DR. FARLEY: Thank you.

DR. COX: So I just would like to emphasize that what we are looking toward is what we are likely to see next year and, even though -- and we have had relatively few B viruses in the United States, and even though if you look at the United States, the majority of them are -- sorry, eight out of 11 are Yamagata lineage viruses, that's not true globally, and the n is very small.

OPERATOR: Next question, Theodore -- I'm sorry, he has disconnected, and once again for questions press *1, please. Robert Couch, your line is open.

DR. COUCH: Well, Nancy, just a comment. I hear you saying what we hope the sequence will be,

but on the other hand, we hope the sequence for this winter would be a Yamagata derivative, and yet Victoria appears to be dominant.

DR. COX: I'm sorry. I don't quite understand your question.

DR. COUCH: Well, it was a comment that we guessed last year that this year our B would be a Yamagata derivative Shanghai, and yet it's turned out to be more Victoria-like than Shanghai. I don't differ with you in hoping that it is correct that the guess for next year would be Victoria, but you did concede that it is something of a guess.

DR. COX: Oh, of course. It always is. I mean, we have -- We can't predict with certainty, but the pattern -- the numbers of strains that we have globally, I think, are greater than the numbers we have had in some previous years, and we also note that we had -- In the vaccine we did have the Yamagata strain, the Yamagata lineage virus. We have Jiangsu/10 in the vaccine this year.

DR. COUCH: I don't think we need any further discussion. I just thought we ought to make

the comment.

DR. COX: Yes. Well, we did predict correctly this year, but we have had very little B activity.

OPERATOR: All right. Next question, Theodore Eickhoff, your line is open.

DR. EICKHOFF: Thank you. Nancy, what do you see as the significance of amantadine resistance in selecting strains for vaccine production?

DR. COX: I don't see any significance at all. So in other words, I brought it up simply because I wanted to emphasize that we are conducting routine surveillance for amantadine resistance, but in terms of vaccine selection, it does not have relevance because for influenza A viruses, of course, we put the HA and NA on the PR8 backbone.

It certainly does have significance for clinicians, particularly with respect to managing institutional outbreaks.

DR. EICKHOFF: Thank you. Just wanted to clarify that.

OPERATOR: Thank you. We are showing no

further questions.

ACTING CHAIR KARRON: Thank you. I think at this time I would like to call Dr. Zhiping Ye from the FDA.

DR. YE: All right. Let's move on next slide 2. The main points of doing this serological study is to see whether the post-immunization of HA antibody to current vaccine confirms the antigenic and the genetic characteristics that has been presented already by Dr. Nancy Cox.

The serological study -- In a serological study, the panels of sera from 2005 and in 2006 influenza vaccine will be tested for their ability to inhibit hemagglutination of current influenza virus isolates.

The post-immunization HA antibody titer of current virus isolates in the panel will be compared to the vaccine strain. For easy understanding, the vaccine strain, at least in the table in which way I am going to present it, either in bold or in colored as blue; where the lower titer of current virus isolates indicating poor antibody inhibition will be

in italic font or colored as red.

Now I will move on to slide 3. As you can see in the slide 3, the serological data I am going to be presenting come from four different centers, which are Australia, Europe, Japan and the U.S. This sera panel will be tested in five different laboratories, which are CBER, CDC, NIBSC in UK, and in Australia, as well as NIID in Japan.

We share the sera panels between several different laboratories and tested these sera panel each within those laboratories. Slide 4.

It seems the majority of the current influenza H1N1 influenza viruses were antigenically indistinguishable from current influenza virus vaccine, and I am not going to show the serological studies or serological data for the H1N1 influenza virus.

Instead, in Slide 4 shows the antigens used for H3N2 serological study. The virus -- The vaccine strain of H3N2 for 2005 and 2006 is New York/5504. Unlike antigen listed in the table in the ferret sera presented by Dr. Nancy Cox, the antigen

for the serological study are relatively few, and has been selected to be representative of the current circulating virus, such as A/Wisconsin/7605, A/Hiroshima/5205, A/Anhui/1239-05, and the rest of the strains -- I am not going to read it.

Now we move on to Slide 5. In terms of the response, I will show you some of the tables, just representative of the results that can come from different centers.

The main purpose -- Again, the main purpose of the serological study is to compare the antibody responses between the different antigens. Slide 5 shows HI antibody response of pediatric population to the H3N2 components of the 2005 and 2006 influenza virus vaccine.

The table I am going to show to you contains the percentage of fourfold increase, the percentage of the people who have above arbitrary cut of antibody titer, like one to 30 or one to 40, but I am really going to focus on the titer that is listed in the center of the table colored with blue or red.

On average every one of the slides, the

vaccine strain, as I said, in bold or in blue, and those are -- Red would represent 50 percent or greater reduction in post-immunization titer as compared to the vaccine strain.

As you can see here, antibody response to the pediatric population to H3N2 components was tested in three centers, CDC, CBER and the UK. Now I will just focus on the panel from CDC.

The CDC sera panel, you can see that we not only test for the A/New York/5504, which is the vaccine strain, but also we tested for A/Brazil/1742, Wisconsin/67/05, Hiroshima/5205, Anhui/1239/05, and North Carolina/13/05.

Except the strain of Brazil/1742/05, the most part of the post-immunization response to the individual who received the vaccine of New York/55/04 were more than 50 percent reduction against A/Wisconsin, A/Hiroshima, A/Anhui, and A/North Carolina. The same result, of course, was obtained from the test of different centers such as CBER and the UK.

So the bottom line from this slide shows

that the majority of the new isolates has reduction of the GMT to the vaccine strain.

Now I will move on to Slide 6. As you can see in Slide 6, that holds true for the adults. This slide shows the adults. So this is similar patterns to the results which is shown in the pediatric. The most part of the immunization response of the adults who were immunized with New York/55/04 were about 50 percent reduction against strains such as Hiroshima/52/05 and Wisconsin/67/05.

Now move on to slide 7. Slide 7 shows a summary of the adult results across the different centers. Again, please focus on the last column on the right, which shows the percentage of GMT of the test of the virus compared to the vaccine strain.

The greater percentage of reduction in this there are, they are more antigenically different of the current strain from the vaccine strain. As you can see here, North Carolina/13/2005, Lyon/21/2006, Gunma/16/2005 has the reduction from 65 to 83 percent compared to the vaccine strain.

Also, the reduction of the -- the

percentage of reduction of Wisconsin is 42 percent, amount of tested serum.

It is true also for the greater than 50 percent GMT reduction of current strain against the vaccine strain, which is listed in the column next to the percentage reduction, which I colored as red. In here, again to emphasize that, this represents the proportion of the GMT which has more than 50 percent reduction compared to those of the vaccine strain.

As you can see, that the post-immunization GMT titer for the most of the part of the new strain was not well inhibited by the antisera that are raised against the vaccine strain, suggesting the replacement of the current vaccine.

Now we move on to B, influenza B, which is the slide 8. Slide 8 lists the antigen for influenza B viruses. There were two HA lineages for influenza B viruses, which are B/Yamagata/1688 in lineage which is our current inactivated influenza virus vaccine, which is B/Jiangsu/10/2003, and another B lineage is the B/Victoria/288 lineage, which contains the Malaysia/2506/2004, Ohio/1/2005. So there are two HA

lineages in this table which we used for serological studies.

Move on to slide 9. Again, HI antibody response to pediatric population to the B components of 2005 and 2006 influenza virus vaccine was tested in three centers, CDC, CBER and the UK.

Except the strain B/Florida/7/2004, the individuals who received the vaccine with B/Jiangsu/10/2003 antigen were more than 50 percent reduction against B/Yamagata lineage, such as B/Florida/7/04 and B/Gansu/9/2005, as well as a reduction against B/Victoria lineage antigens such as B/Malaysia/2506/04 and B/Ohio/1/2005, as compared with those to the vaccine strain.

So the same results are showing from the study at CBER and the UK.

Slide 10: So you can see in Slide 10 the results of the serological panel from adult population tested by CDC, part of a post-immunization response of adults who received the immunization with B/Jiangsu was more than 50 percent of reduction, against B/Victoria/288-like viruses such as the B/Ohio and the

B/Malaysia/2504.

Now to move on to Slide 11. Slide 11 shows the summary of all the adults' results across all the centers, which I mentioned are five centers. Again, please focus on the last column on the right, which shows the percentage reduction of the GMT of a tested virus as compared to the vaccine strain.

The percentage GMT reduction to the B/Malaysia/2506/2005, B/Ohio/1/2005, and the B/Guangdong/321/2005 was from 50 percent to 67 percent.

Looking at more than 50 percent of reduction between the different sera tested in the different labs, the most part of post-immunization responses of the adults who were immunized with B/Jiangsu/10/2003 was about 50 percent reduction against the different HA lineage such as B/Malaysia/2506, B/Ohio/1/2005, B/Guangdong/321/2005, which were found in more than -- found most in the recent isolates, indicating the current vaccine did not cover well to the current B isolates.

Now move on to the last slide. Here is

the summary. In summary, study with sera collected after immunization with the current vaccine shows that for H1N1 representative recent isolates were well inhibited as compared to the vaccine strain A/New Caledonia/20/99, the data I didn't show in my slide.

For H3N2, A/Wisconsin/67/2005-like viruses, less well inhibited compared to the vaccine strain with some of the exceptions such as the A/Brazil/1742/2005 and Anhui/1239/2005.

Now for the B strain, the representative recent Yamagata/1699 lineage viruses, generally well inhibited compared to the vaccine strain. However, the representative recent virus that is in B/Victoria/2/1987 lineage such as B/Yamagata/2506/2004-like strain were poorly inhibited compared to the vaccine strain.

I will stop here.

ACTING CHAIR KARRON: Okay. We will take questions for Dr. Ye. Press *1. Ask questions.

While we are waiting for people to log in, I actually have a question about Slide 5. My question is, it seems to me that the UK data are discordant

with the data from CDC and CBER, in that children seem to actually have reasonable responses to Wisconsin. I was just wondering if there is any explanation for that or whether there was perhaps discussion of that at the WHO meeting.

DR. YE: Actually, the test in the different centers in slightly -- although we used the same method for the HI test, but in a different condition, a different preparation may have different -- slightly different results.

I think another difference, the possible explanation is that initially we sent the sera to CDC, and we do not have enough sera for UK, and then later on we received additional sera panels, and we sent that to UK. So the UK panel is not exactly the same as the panel that is studied in CDC and CBER.

As you can see in Slide 5, they have 19 samples, where CBER would have 30, and CDC usually is 24 out of 30.

ACTING CHAIR KARRON: Okay. I'm just wondering, would you happen to know, were those perhaps older children then that were sent in the

panel to the UK?

DR. YE: The children -- The age of the children is the same, but only the different -- slightly different samples. We did not preselect the pediatric serum. So probably this reflects the different individuals.

ACTING CHAIR KARRON: Okay. Additional questions for Dr. Ye?

OPERATOR: On the phone, we have a question from Robert Couch. Your line is open.

DR. COUCH: Dr. Ye, I guess my first question -- I think I know the answer, but just that there are some errors in the table that I don't think we need to stop and correct, but just to acknowledge on your part.

For example, if we look at Table 5 and the CBER data on Anhui, the GMT pre- is 12, the GMT post- is 12, and that shouldn't be with 82 percent rises and the 68 post.

DR. YE: I noticed some errors, and you can see in Slide Number 6 there are some errors on the study centers. I am sorry about that.

DR. COUCH: Yes, and the same was true with the pediatric population for B where we are looking at no rises on the UK sera, and yet we have 95 percent equal to or greater than 1 to 40. But I don't think we need to dwell on that, but to acknowledge that.

I just wanted to make the point that some of the group won't be surprised to hear from me, and that is that the data vary, as we all know. My recollection of earlier data when we have looked at the B/Yamagata derivatives and looked at B/Victoria responses among adult populations that it has always been reasonably good.

For example, if you look at the Table 10 and the USA data -- I think you have indicated that was CDC data -- the disparity is a little bit surprising, but the B/Yamagata strain, the Jiangsu, had -- if you look at the B/Malaysia result, the 17 percent rises must be wrong, but the post is 83, which is not a whole lot different than the post from Gansu and from the homotypic strain, even though it is surprisingly lower for Ohio/1 and Guangdong. But it's

that generality of you do very reasonably well with either of the derivatives in adults with cross-reacting antibodies.

So that you might say, well, if we miss on selecting the B, it may not be so critical for adults. But on the other hand, if you look at Slide 9, every time we look at children with regard to the cross-reactivity, it doesn't exist. The children, each time they receive a Victoria and you look at Yamagata derivative or receive a Yamagata derivative and you look at Victoria, they look like the ferrets. They just don't carry any cross-reacting antibodies.

So that if we miss on selecting that strain, the most vulnerable population for having missed will be the pediatric population, and while they are not a big population for mortality, those school age children represent the major peak for influenza B epidemics every time we have one.

So some of the group have heard me speak before, and I'll bring it up again maybe, but I continue to have concern. I guess it's three years in a row that we end up being a little bit too much at

the mercy of our guess for influenza B in terms of the kind of protection that we would like to be more confident we are inducing.

And as Dr. Cox and all of us know, it's an educated guess, and the educated guess is for Victoria this year, but maybe I'm emphasizing it a little too much, but nevertheless, it's a guess.

That's more of a comment, not a question.

OPERATOR: We are showing no further questions.

ACTING CHAIR KARRON: Okay. Dr. Ye will now speak to us about the availability of strains and reagents.

DR. YE: Now I am going to present to you the status of candidate vaccine strains and related potency reagents. Next slide.

Now this slide shows the influenza A-H1N1 influenza viruses. The current vaccine strain is New Caledonia/20/99, a reassortant which is a reassortant between wild type A/New Caledonia/29/99 and the PR8. The reassortant is IVR-116. This virus grows pretty well in eggs.

Currently, we do not have a new antigenically divergent strain available this time for the candidate strain.

Now we move on to next slide, influenza H3N2 viruses. The current vaccine for H3N2 is New York/55/04, which is a Caledonia/07/2004-like strain. The reassortant NYMCX/155 again is a reassortant mutant wild type New York/55/04 and PR8, and this virus again grows pretty well in eggs.

There are two candidate strains currently under investigation for the possible use of a reassortant. One, as you already noticed, is the A/Wisconsin/67/05, A/Hiroshima/52/2005. Again, the preparation of the reassortant of those two strains is ongoing.

Now we move to influenza B viruses. The current vaccine for influenza B is a B/Shanghai/361/02-like strain, which is Yamagata lineage. There are three strains used in vaccine. One is Shanghai/361/02 itself; B/Jiangsu/10/2003 and B/Jilin/20/2003, which is used in live attenuated influenza virus vaccine. All of them grow moderately

in eggs.

Now we move on to influenza B candidate strains. Again I mentioned that there are two HA lineages for influenza B viruses. Victoria lineage is the representative for the base lineage are two strains: B/Malaysia/2506/04 and B/Ohio/01/2005.

The B/Malaysia/2506/04 is current vaccine strain for southern hemisphere, and this virus grows moderately in eggs; where the Ohio/01/2005 grows at low to moderate.

Another lineage which is Yamagata lineage, the representative candidate is B/Florida/07/04, and this virus grows low to moderate rate in eggs.

Now we move on to potency reagents. The potency reagent currently available for A from CBER follows. For H1N1, A/New Caledonia/2099, as you can imagine. Otherwise, for H3N2, New York/55/04, currently available from CBER, but if a new strain is chosen such as A/Wisconsin/67/05-like strain going to be chosen, the reagents will be prepared, and the reagent will be available in May at the earliest.

Now on the next slide reagents currently

available for B, for influenza B. The reagents for B/Shanghai/361/02-like strain, which is available from CBER: The strain is B/Jiangsu/10/2003, where for Yamagata lineage CBER has B/Hong Kong/330/2001, B/Hong Kong/144/2002, and B/Shanghai/07/1997.

For B/Malaysia/2506/2004, since this strain is the current southern hemisphere vaccine strain, so the reagents for this particular strain is available from TGA in Australia, NIBSC in UK and NIID in UK. If we choose this strain, the fresh, new reagent is going to be prepared, and that will be available in May at earliest.

I will stop here for the questions.

ACTING CHAIR KARRON: Are there questions for Dr. Ye?

OPERATOR: Thank you. We have a question from Alexander Klimov. Your line is open.

DR. KLIMOV: Yes. Hi. I just wanted to make a statement to Dr. Couch. You notice that in the adult population in some serology data presented by CBER, actually, against Malaysia. In that case, Dr. Couch was talking the percentage of people with HI

type -- against Malaysia should be 38, not 98, as indicated in the Table 10 of the presentation. So it is probably just a typo.

ACTING CHAIR KARRON: Thank you. Are there other questions or comments?

OPERATOR: We are showing no further questions.

ACTING CHAIR KARRON: Okay. Our next speaker is Mr. Albert Thomas of sanofi pasteur, who is representing the vaccine manufacturers. Mr. Thomas.

MR. THOMAS: Good afternoon. I am just checking if you can hear me.

ACTING CHAIR KARRON: Yes, we can hear you.

MR. THOMAS: My name is Albert Thomas. I am the Director of Viral Manufacturing for sanofi pasteur.

I would first like to thank the Committee for the opportunity to present today, and would like to begin by talking about some of the critical factors that are involved with influenza vaccine supplies and how the strain selection process can impact each of

these factors. First slide.

The first critical factor is the growth potential of each monovalent strain seed virus. Obviously, there are many factors that can impact the number of doses of influenza vaccine that can be produced, such as the overall capacity that is available to each manufacturer, the average yield of all three monovalent strains, but most typically the number of doses of trivalent vaccine is limited by the yield of the poorest growing monovalent strain.

For example, a manufacturer may be successful in producing 40 million doses of the H1N1 monovalent strain, 40 million doses of the B strain, but if only 20 million doses of the H3N2 strain can be produced, there will only be 20 million doses of trivalent vaccine available for immunization.

The most critical overall factor is time. the timing for influenza vaccine manufacturing is limited at the beginning by the timing of the strain selection process, and is then limited at the end by the need to distribute and administer the vaccine prior to the onset of the influenza season.

Thus, the actual time to develop production seeds, manufacture the monovalent, formulate the trivalent vaccine, fill, package, release and ultimately distribute is quite limited. Also, please keep in mind that production seeds typically require at least four weeks from time of receipt to development and release prior to beginning large scale manufacturing.

The availability of potency test reagents are another factor that must be taken into account. The potency of each monovalent component lot must first be determined prior to formulation of the trivalent vaccine, and that is done via single radial amino diffusion, which requires a strain-specific reference antigen and antiserum.

These two potency test reagents must first be manufactured and standardized for each new strain prior to the initiation of trivalent formulation. The time to prepare and standardize the reference reagents can take anywhere from eight to 12 weeks.

Please turn to the next slide.

Page 2 of the presentation depicts a

typical fine line in the manufacture of trivalent influenza vaccines. The timeline assumes that there is one strain change from the previous to the current year, and the new strain here is listed as strain 3.

The upper half of the timeline is related to the production of the individual monovalent components. The lower half lists the timing of the preparation of the reference reagent as well as the formulation of the bulk trivalent vaccine, filling, packaging, and ultimate distribution.

As mentioned before, the time to distribute the vaccine is fixed, so that distribution can begin typically in the early August time frame and continue until early November. The past two seasons have been a bit of an exception to the typical timing, in that distribution of vaccine has extended later into the year.

So the overall timing of influenza vaccine is, again, limited at the beginning by strain selection and limited at the end by the need to distribute vaccine in time for immunizations.

At the top of the timeline, an arrow was

included in mid-February to highlight the timing of today's meeting on strain selection. You may have also noticed that the timeline shows that production of one monovalent strain is already underway.

Manufacturers may choose to begin production of one of the strains at risk, and that risk is a strain that may not ultimately be included in the vaccine formulation for the coming year. The reason why manufacturers may choose to do this is due to the limited time available for production of the monovalent component.

Thus, at the time of the mid-February VRBPAC strain selection meeting, manufacturers are looking to begin production of the second monovalent strain. Assuming the availability of an appropriate production seed, manufacturing of the second strain typically begins immediately following the strain selection announcement.

Once a production seed is available for the third strain, manufacture of that strain would also commence. This timing assists with ensuring a balanced production plan of all three monovalent

components.

In parallel with the large scale manufacture of the monovalent components is the production and standardization of the potency test reagents. So the reagents are available; the yield of any new strain is announced.

Once the reagents are available, manufacturers can begin balancing production of all three monovalent strains, with the goal of having an equal dose equivalence of each strain at the end of the production campaign.

Formulation of the trivalent vaccine can also begin once the potency reagents are available, which would then be followed by filling, packaging, and distribution. Next slide, please.

Page 3 of the presentation lists the current manufacturing status. As previously mentioned, some manufacturers may have chosen to begin production of one strain at risk. For this year, production of the A/H1N1/New Caledonia strain was initiated at risk.

At this time the manufacturers are also

evaluating the growth potential of any new potential strain candidates. Next slide, please.

In conclusion, a successful influenza manufacturing and ultimate vaccination program is based on cooperation among all the involved parties. The consideration of both antigenic match, the availability of seed candidates, including high growth reassortants, as well as the potential growth of each candidate strain is necessary to ensure a successful influenza vaccine supply scenario.

A good example of the success of this cooperation is the increased availability of egg isolates and high growth reassortants that manufacturers can evaluate for potential growth that are antigenically similar but may have different -- very different growth characteristics in large scale production.

During the evaluation of potential strains for the 2004 and 2005 season, manufacturers were able to select from three A/Shanghai/361/2002-like strains. Given that the manufacturers of the inactivated influenza vaccine all chose the B/Jiangsu/10/2003

strain again shows that antigenically similar strains may have significantly different growth characteristics.

The increased availability of both egg isolates as well as high growth reassortants are significant contributors to improving the quality of influenza vaccine.

In summary, it is necessary to consider the various factors, such as appropriate selection of strain based on antigenic match, as well as availability of seed candidates and high growth reassortants in order to best ensure adequate supply of influenza vaccine.

In conclusion again, I would like to thank the Committee for the opportunity to present the viewpoints from the influenza vaccine manufacturers at today's meeting.

ACTING CHAIR KARRON: Thank you, Mr. Thomas. We'll take questions. While we are waiting for people to ring in, I have one for you, which is: I know that nationally our vaccine manufacturing capacity has increased from about 80 million doses to

about 120 million doses, is my understanding.

My question is. How, if at all, does that impact the timeline that you have described?

The second question, because this is clearly something that this Committee has discussed in the past: How, if at all, would it impact the creation, let's say, of a quadravalent vaccine that had two influenza B candidates?

MR. THOMAS: Speaking first to the overall capacity, my opinion is, that would not change the timelines. It would just be adding additional capacity really following that same timeline. So if there were truly a manufacturing capacity that was of greater capacity, the amount of influenza vaccine -- the timing probably would not change, but additional quantities would be available at those same time points.

Then in answering the question regarding the potential for four strains, obviously, that would quickly reduce the amount of vaccines being distributed by at least 25 percent, as well as add in the additional complications of another strain to be

selecting and then also the preparation of the reference antigen and purified HA for the potency testing, as well as each manufacturer may also have to make some changes to their production processes to accommodate that fourth strain.

ACTING CHAIR KARRON: Thank you. Other questions?

OPERATOR: Again, do you have any question? One moment, please. Theodore Eickhoff, you may ask your question.

DR. EICKHOFF: Thank you. Mr. Thomas, recalling what Dr. Ye just said earlier about the availability of potency test reagents, if the Committee winds up changing two strains in the vaccine, which seems possible, and the potency test reagents are not available until May at the earliest and perhaps until June, how does that affect your vaccine production?

MR. THOMAS: I'll refer back to, I believe, the 2004-2005 campaign, in which case there were two strain changes also. The timing of the reference reagent that Dr. Ye had mentioned is typical

in a campaign, in which case there would be two strains that would change.

What would happen is each manufacturer, again, would begin production of each of the strains pretty much probably as soon as they can, as soon as they have production seeds available, and would continue producing that strain until they would have the next seed, and they would utilize some estimates of potency, perhaps based on protein or some other method, to try to estimate, again, how many doses they are producing.

Obviously, it is a concern with more than one strain change. It does put more uncertainty in the total bar for number of doses that you are producing at any given time, and obviously, as soon as the reference reagents are available, manufacturers would then begin the strain balancing, in which case they would try to equal out the manufacturing of all three strains.

DR. EICKHOFF: Thank you.

OPERATOR: Our next question comes from Monica Farley.

DR. FARLEY: Yes, thank you. Would the choice of B/Malaysia affect in a positive way the timeline due to the fact that it had been the choice for the southern hemisphere formulations and there might be some reagents that are available through other agencies?

MR. THOMAS: I'm making an assumption here that maybe someone else on the Committee would like to confirm. But, obviously, since this strain was available and was selected for the current southern hemisphere formulation, it would be assumed that manufacturers would have had an opportunity to work with that seed to have production seeds ready for manufacturing.

So in that case, there would be some advantage in that they could begin manufacturing quickly, but for release of the vaccine for the United States I would assume that CBER would require a CBER-distributed reference antigen as well as -- though you would still have that delay by the time you had that produced.

If other reagents were available from

other laboratories, it would be possible to maybe utilize those to estimate yield along the way, which may give you a better estimate than a method such as utilizing protein.

OPERATOR: We will go to the next question, sir.

ACTING CHAIR KARRON: Could we just hold the next question for one moment so that Dr. Baylor can comment.

DR. BAYLOR I'll just comment on that as far as the requirements to use the CBER reagents. I mean, we can consider using those other reagents if they are available. So I don't think we should assume that we would necessarily require that. We could have discussion about that, especially dealing with the timing.

ACTING CHAIR KARRON: Thank you.

OPERATOR: Thank you. Robert Couch, you may ask your question.

DR. COUCH: Well, actually, mine is a comment, and maybe the question that I had was close to Ted Eickhoff's. But in thinking about the

quadravalent vaccine that Ruth Karron brought up with two B components, we would all say that it would be important that we not have two new Bs, if at all possible, so that the carryover would be from a Yamagata and add to it a Victoria. That would be the reasonable proposal to get -- not upset the vaccine timeline, but then to take it on, as Ted said, to where do we run into trouble.

See, there are so many factors that impact this timeline, including the seeds and the reagents that have been referred to, but a lot of that is inherent in selecting a new strain.

What sort of freedom -- I wonder if Dr. Thomas would comment -- do we have with that, you know? In other words, two strains could give you a problem. Does three break the camel's back, if we wanted to change all three?

MR. THOMAS: Actually, I think one single strain change could have a detrimental impact, if it is not a very good grower. That is the risk we always run into.

DR. COUCH: That's a risk always for a

single strain, as we pointed out, with your reagents and the seeds.

MR. THOMAS: Right.

DR. COUCH: Assuming they went well, do you have a strain change number that would begin to significantly impact us?

MR. THOMAS: I think we have seen in the past, again, it will depend on how many or how well each individual strain will be growing. Typically, when we have two strain changes, it is a struggle to maintain your manufacturing and estimate your potencies until you have the reagents available.

Again, I will just comment quickly here again on a potential four-strain vaccine. I'm assuming there would be licensing and regulatory implications and, you know, which potency would be formulated that would have to be answered prior to that -- prior to beginning looking at some of the specifics of how we would incorporate that.

Again, from the manufacturing point of view we would always look at minimizing the number of strain changes, because, obviously, any history we

have with a strain allows us to estimate what that production capability will be going forward.

ACTING CHAIR KARRON: We have a comment from the floor.

OPERATOR: We do have one more question from Bruce Gellin.

ACTING CHAIR KARRON: Can we hold that question for one moment. We just have one comment from the floor.

MS. COELINGH: Just a quick question. Kathleen Coelingh from Medimmune.

In discussion of B/Malaysia, the question about choosing the B/Malaysia strain, I am assuming that that would allow manufacturers to use the Ohio strain, if they so choose. We evaluate the strains not only for growth in eggs for the live attenuated vaccine, but also for performance in different assays.

There are lots of different things that we are evaluating. So if antigenically it is a B/Malaysia, I'm assuming it would be -- an Ohio would be acceptable also.

DR. WEIR: Yes. I mean, I think we

generally make a recommendation that would be recommending a B/Malaysia-like, and the Ohio was considered to be a Malaysia-like virus.

ACTING CHAIR KARRON: We can go back to our call-in questions at this time.

OPERATOR: Bruce Gellin, you may go ahead.

DR. GELLIN: Sure. My question was similar to Monica's, and I guess -- to do whatever can be done --

OPERATOR: I believe Bruce Gellin is on a cellphone, and he is breaking up right now.

ACTING CHAIR KARRON: I think we will have to go on to the next question and, if Bruce is able to connect better, he can call in again.

OPERATOR: Again, *1 if you do have any questions. At this time, I am showing no further questions.

ACTING CHAIR KARRON: Okay. At this point we will take a break. I think what we will perhaps do is just take a break until about 3:15. We will reconvene at that time. So we are on break.

(Whereupon, the foregoing matter went off

the record at 3:06 p.m. and went back on the record at 3:16 p.m.)

OPERATOR: Good afternoon, and thank you for standing by. Mr. Walsh, you may go ahead and proceed.

MS. WALSH: Michele, before we start, can you just let us know, confirm that everyone is still on the line and we didn't lose anyone.

OPERATOR: Bruce Gellin -- I believe he is the only one I have disconnected, ma'am.

MS. WALSH: Thank you very much.

ACTING CHAIR KARRON: At this time, we will begin the open public hearing. Christine, I believe you have an announcement.

MS. WALSH: Thank you, Dr. Karron. As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee.

I have received one written request from B. Sachau, who was not able to attend the meeting, for

comments provided to the Committee members posted in the public hearing notebook at the registration desk, and copies are available upon request at the registration desk.

Is there anyone in the room who would like to address the Committee at this time?

I see no response and, Dr. Karron, I turn the meeting back over to you.

OPERATOR: Ma'am, we do have one question. Philip LaRussa, you may go ahead.

DR. LaRUSSA: It seems to me we have this discussion about two strains of influenza B every year, and some folks think every year at this time that it is not practical to do it.

Maybe we should start a discussion now about whether we want that to be the eventual goal, since we seem to have to deal with this problem, and manufacturers have to build up capacity so that we could have larger valent vaccine, number of doses made.

ACTING CHAIR KARRON: I think at this time, Philip, probably what we should do is I think we

will have that discussion, but I would rather go ahead and have Dr. Weir present the strain selection options, and then as part of the general discussion let's talk about that issue.

DR. LaRUSSA: Yes. I'm not suggesting we do it now. I'm suggesting that at our next meeting we start this discussion so we don't do the same thing next year in February.

DR. WEIR: Okay. Thank you. All right. So I guess we are ready for the Committee discussion portion of our meeting today, and I have two remaining slides on my presentation, the last slide and the next to the last slide.

The next to the last slide essentially outlines what we have also presented, I think, as a Word document for the questions to Committee, but basically we are asking now to discuss the strains that should be recommended for the antigenic composition of the 2006-2007 influenza virus vaccine, and base this discussion on the following: The epidemiology and the antigenic characteristic of influenza virus strains circulating in human

populations; the serologic responses to circulating influenza virus; the person immunized with current influenza virus vaccines; and, of course, the availability of suitable vaccine candidate strains.

In the last slide, I listed a series of options for strain composition, things that can be considered in this discussion. For influenza A/H1N1, one option is to retain the current vaccine strain recommendation, A/New Caledonia/20/99/H1N1-like virus.

Alternatively, you could consider replacing the current vaccine strain with an alternative H1N1 isolate, although I don't think we heard any data today to suggest what that might be.

Second, for the influenza A/H3N2 component of the vaccine, one option is to retain the current strain recommendation, i.e., a A/California/7/2004/H3N2-like virus. Another option is to replace it with an A/Wisconsin/67/2005/H3N2-like virus or, alternatively, another H3N2 isolate which I'm not sure we heard much data to support.

Finally, for an influenza B, the options are to retain the current B/Shanghai/61/2002-like

virus or replace it with an alternative virus with the same B/Yamagata/16/88 lineage.

The other option is to replace the influenza B component with the B/Malaysia/2506/2004-like virus or some other virus from the B/Victoria/2/87 lineage.

So I will stop here and turn it back to Dr. Karron for the Committee discussion.

ACTING CHAIR KARRON: Thank you. At this time, I think I would just like to open it up to some general discussion. So if you would call in with your questions or comments.

OPERATOR: Showing no questions at this time.

ACTING CHAIR KARRON: Well, I think, really, if there are no questions, what we will do is proceed with the vote on each of our strains. We can certainly have discussion in advance of voting on each of the strains, if people want to discuss each of these.

So I think we will, obviously, begin with the H1N1 strain. What I would like to first do is

make sure that there is no discussion on that particular strain, no issues that people want to bring up with regard to H1N1. So we will just pause a minute and see if there are any questions or comments.

Okay, I think, if there are no questions, what I will entertain then is a motion from someone on the Committee regarding the H1N1 strain. I'm actually wondering if the operator could inform us if everybody is still on the call, because we do need -- We actually do need a motion of the Committee for the H1N1 strain, and then we can vote on that strain.

OPERATOR: Everybody is on with the exception of Bruce Gellin.

ACTING CHAIR KARRON: Okay. So I need someone to speak up.

OPERATOR: We do have two questions now. Melinda Wharton, you may ask your question.

DR. WHARTON: I would like to make a motion that we retain the current vaccine -- the current H1N1 strain, the New Caledonia/20/99.

ACTING CHAIR KARRON: Thank you. Could I have a second for that motion?

OPERATOR: Ma'am, just let me know when you would like to go to the next question.

ACTING CHAIR KARRON: No. We actually need a second for that motion in order to then have all of the members vote. So I need one of the members to call in with a second for the motion for A/New Caledonia's H1N1 strain.

OPERATOR: Okay, we have several people. We have four people that have queued up. Would you like me to ask them?

ACTING CHAIR KARRON: Please.

OPERATOR: Monica Farley, you may go ahead.

DR. FARLEY: Well, the first thing I would suggest is maybe you can release us all, and let us all be able to speak so there won't be these long lags during this period.

ACTING CHAIR KARRON: Yes.

DR. FARLEY: Just for this voting time frame. That might help.

Then I will second the motion.

ACTING CHAIR KARRON: Monica, did you make

the motion?

DR. FARLEY: No.

ACTING CHAIR KARRON: I'm sorry. Forgive me. Thank you, Monica. And I think that is an excellent suggestion. Is it possible for us to just open the lines completely?

OPERATOR: We sure can. One moment.

ACTING CHAIR KARRON: Thank you. Thank you, Michele.

OPERATOR: Ma'am, all the lines are open at this time.

ACTING CHAIR KARRON: Okay, thank you.

DR. GELLIN: This is Bruce. I want to "third" the motion to prove that I am actually listening here.

ACTING CHAIR KARRON: Thank you, Bruce. We appreciate it.

Okay. At this point, we are voting on the H1N1 strain. There has been a motion that we retain the A/New Caledonia/29/99, and I am going to call each member in turn and ask you to vote yes or no.

Dr. Couch, I am going to start with you.

DR. COUCH: Yes.

ACTING CHAIR KARRON: Lieutenant Commander Hachey.

LT CMDR HACHEY: Yes.

ACTING CHAIR KARRON: Dr. Royal?

DR. ROYAL: Yes.

ACTING CHAIR KARRON: Dr. Modlin? Dr. Modlin? Okay, we will move on. Dr. Self?

DR. SELF: Yes.

ACTING CHAIR KARRON: Dr. Word.

DR. WORD: Yes.

ACTING CHAIR KARRON: Dr. LaRussa?

DR. LaRUSSA: Yes.

ACTING CHAIR KARRON: Dr. Gellin?

DR. GELLIN: Yes.

ACTING CHAIR KARRON: Ms. Province?

MS. PROVINCE: Yes.

ACTING CHAIR KARRON: Dr. McInnes? She may not be here. Dr. McInnes? Dr. Farley?

DR. FARLEY: Yes.

ACTING CHAIR KARRON: Dr. Wharton?

DR. WHARTON: Yes.

ACTING CHAIR KARRON: And Dr. Eickhoff?

DR. EICKHOFF: Yes.

ACTING CHAIR KARRON: Thank you. Oh, and I also vote yes. I'm sorry, hold on for just one second. I also need -- Although it is not part of the formal tally, Dr. Hetherington, I need your vote.

DR. HETHERINGTON: Right. I am a non-voting member, but if I were to vote, I would vote yes.

ACTING CHAIR KARRON: Thank you.

DR. McINNES: Dr. Karron.

ACTING CHAIR KARRON: Yes.

DR. McINNES: This is Pamela McInnes. Could you please -- Can you hear me?

ACTING CHAIR KARRON: Yes, I can.

DR. McINNES: Sorry, it wasn't clear to me that you could. Thank you.

ACTING CHAIR KARRON: But I couldn't hear you before, Pamela. So did you -- Can we go back to you for your vote on H1N1/A/New Caledonia?

DR. McINNES: Yes.

ACTING CHAIR KARRON: Thank you. Okay.

So the next strain that we are considering is the H3N2. I first -- Especially now that we have all of the lines open, I would like to ask if there is any more discussion about the H3N2 strain that people would like to have.

Okay. In that case, I need a motion for the H3N2 strain. As you heard from Dr. Weir, the possibilities are to retain the A/California/2004-like virus or to replace that with A/Wisconsin/67/2005.

Could I get a motion from one of the Committee members?

DR. LaRUSSA: This is Phil LaRussa. I'll make a motion to replace the current strain with A/Wisconsin/67/2005.

ACTING CHAIR KARRON: Thank you very much. Do we have a second for that motion?

DR. EICKHOFF: Ted Eickhoff. I will second.

ACTING CHAIR KARRON: Thank you. Okay, and Dr. Eickhoff, this time we will begin the voting with you.

DR. EICKHOFF: Well, I'll vote yes.

ACTING CHAIR KARRON: I guess that's pretty obvious. Okay. Dr. Wharton?

DR. WHARTON: Yes.

ACTING CHAIR KARRON: Dr. Farley?

DR. FARLEY: Yes.

ACTING CHAIR KARRON: Dr. McInnes?

DR. McINNES: Yes.

ACTING CHAIR KARRON: Ms. Province?

MS. PROVINCE: Yes.

ACTING CHAIR KARRON: Dr. Gellin?

DR. GELLIN: Yes.

ACTING CHAIR KARRON: Dr. LaRussa?

DR. LaRUSSA: Yes.

ACTING CHAIR KARRON: Dr. Word?

DR. WORD: Yes.

ACTING CHAIR KARRON: Dr. Self?

DR. SELF: Yes.

ACTING CHAIR KARRON: Dr. Modlin? Okay. Dr. Royal?

DR. ROYAL: I vote yes.

ACTING CHAIR KARRON: Lieutenant Commander Hachey?

LT CMDR HACHEY: Yes.

ACTING CHAIR KARRON: And Dr. Couch?

DR. COUCH: Yes.

ACTING CHAIR KARRON: And I also vote yes, and Dr. Hetherington?

DR. HETHERINGTON: Yes.

ACTING CHAIR KARRON: Thank you. Okay. We are now going to move on to the B strains, and here I imagine that there may be a bit more discussion.

So first, are there any questions or comments about B selection?

DR. KLIMOV: This is Dr. Klimov from the Influenza Branch. I would like to pay your attention -- You know, the majority of the data which Nancy Cox presented were from our center at CDC in Atlanta. She mentioned on page 23 there is a family table of different influenza virus types and subtypes which have been characterized by different WHO centers and many other WHO cooperating laboratories.

I would pay your attention that, in spite of the fact that so far in the U.S. we were able to test more Yamagata lineage viruses than B/Victoria-

like viruses, but if you look at the first column on the page 23 of the package, you will see that totally from the North American, which includes the U.S., a few strains from Mexico and a lot of strains from Canada, you can see that totally we have 100 influenza B viruses, of which 88 are from B/Victoria lineage and only 12 are from B/Yamagata lineage.

For example, Canada has a reasonable number of influenza B viruses circulated this year, and most of them, almost all of them, are from the B/Victoria lineage.

That is my brief comment to the situation. Thank you.

ACTING CHAIR KARRON: Thank you. Other comments or questions?

DR. COUCH: This is Couch again. That was actually -- Dr. Klimov emphasized one of the points I was making earlier, that this past -- so far this winter, I should say, the B/Victoria is dominant in North America, but our vaccine was a B/Yamagata strain.

ACTING CHAIR KARRON: Actually, at this

point before we have a motion and before we vote, I am going to ask Dr. Karen Midthun to make a comment about the issue that Phil LaRussa brought up earlier and that has been discussed on multiple occasions by this Committee, which is really the issue of a quadravalent vaccine, including potentially two B components in the future. So, Dr. Midthun?

DR. MIDTHUN: Sure. I think that we have heard several years in a row the question of, gee, you know, in some cases it would be nice to have two B strains and have a quadravalent vaccine, and I think that what might be helpful is for us to consider having a follow-on meeting.

Perhaps we could consider a workshop where we could bring a lot of partners to the table, because I think there are many, many things one needs to consider.

One needs to consider what is the need to do this? What are the benefits? What are the potential pitfalls? There are a lot of issues in terms of what is the vaccine manufacturer capacity? Do you end up having fewer doses, if you go to the

quadravalent? Would it take you longer to have the vaccine ready, because you have to have four monovalents that you then blend and test and have to make reagents for and test?

You also have the issue of global vaccine manufacture and that we have a lot of B vaccine manufacturers or international multi-global companies and that the vaccine that they make in one area, they would like to be able to market in other areas. So I think we have global partners who we need to be mindful of here.

So I think that perhaps a workshop might be a vehicle that would bring the manufacturers together to talk about logistics. One could have -- you know, invite many people, obviously, from wherever, VRBPAC, the Advisory Committee on Immunization Practices, National Vaccine Advisory Committee, you know, people from WHO. Really, a lot of people might have interest, and it would be interesting to bring the different issues to the table.

As part of that, you know, we, of course,

also would have regulatory issues. That's correct. I think we can address those as well in terms of what do we think would be needed, if that were a direction that we wanted to pursue.

So that is the comment I wanted to make with regard to that. Norman -- Dr. Baylor, do you have anything that you would like to add?

DR. BAYLOR: No. I think that sounds enough.

DR. GELLIN: This is Bruce. Could I add one little piece to that?

ACTING CHAIR KARRON: Yes, please.

DR. GELLIN: Again, from the perspective of pandemic preparedness, as this Committee and a lot of people know, we are trying to increase capacity substantially, and I think that one point of that -- and I think it would come out as part of that workshop -- is that a great increase in capacity would give us a lot more flexibility.

ACTING CHAIR KARRON: Thank you.

DR. COUCH: Couch again. Could I just make one quick comment, and to remind everybody, as I

think I have said before, that there is a precedent for the quadravalent vaccine, and actually it occurred long enough ago that I can't even remember if I was involved in the decision or not. But there were two B components, for the kinds of reasons of concern that we are talking about here.

The second is that the workshop is fine, but it sure would be nice to have a whole lot of data that would more specifically address the question of where we stand immunologically on concerns for various populations, if one or the other possibilities existed.

ACTING CHAIR KARRON: Other comments? I would actually like to make a comment, which is that, you know, having heard these data now for several years running, my personal sense is that there is less of an issue about a second B component this year than there has been in previous years.

I think last year was particularly -- we had a particularly difficult time in deciding on a B component. However, I think the issue has arisen in the past and will absolutely continue to arise, and I

think maybe could be dealt with in exactly the way that Dr. Midthun is proposing.

Are there any other questions or comments regarding the B strain? Okay. Then at this point I need a motion for the B component of this year's vaccine. Don't all talk at once, but somebody say something.

DR. LaRUSSA: This is Phil LaRussa. I'll make a motion to replace the current strain with B/Malaysia.

ACTING CHAIR KARRON: Okay. Do we have a second for that motion?

DR. EICKHOFF: Ted Eickhoff. I will second.

DR. FARLEY: This is Monica Farley. Should we say B/Malaysia-like virus or is that necessary?

ACTING CHAIR KARRON: Yes, we should say that. Thank you.

DR. LaRUSSA: Okay, I'll say that.

ACTING CHAIR KARRON: Okay. All right. So the motion we have and that is seconded is for

replacing the current B strain with a B/Malaysia/2506/2004-like virus.

This time, Dr. Couch, I will start the voting with you.

DR. COUCH: My vote is because my option is not there, but among the options we have I will certainly support changing to B/Malaysia.

ACTING CHAIR KARRON: Thank you. Lieutenant Commander Hachey?

LT CMDR HACHEY: Yes.

ACTING CHAIR KARRON: Thank you. Dr. Royal?

DR. ROYAL: I vote changing to B/Malaysia-like virus.

ACTING CHAIR KARRON: Okay. Dr. Modlin? Dr. Self?

DR. SELF: Yes.

ACTING CHAIR KARRON: Thank you. Dr. Word? Sorry, Dr. Word, I didn't hear you.

DR. WORD: Yes.

ACTING CHAIR KARRON: Thanks. Dr. LaRussa?

DR. LaRUSSA: Yes.

ACTING CHAIR KARRON: Thank you. Dr. Gellin?

DR. GELLIN: Yes.

ACTING CHAIR KARRON: Ms. Province?

MS. PROVINCE: Yes.

ACTING CHAIR KARRON: Dr. McInnes?

DR. McINNES: Yes.

ACTING CHAIR KARRON: Dr. Farley?

DR. FARLEY: I vote yes.

ACTING CHAIR KARRON: Thank you. Dr. Wharton?

DR. WHARTON: Yes.

ACTING CHAIR KARRON: Dr. Eickhoff?

DR. EICKHOFF: Yes.

ACTING CHAIR KARRON: Thank you. I also vote yes, and Dr. Hetherington?

DR. HETHERINGTON: Yes.

ACTING CHAIR KARRON: Thank you. At this time, are there any other comments that either Committee members would like to make, or individuals from the FDA or individuals sitting in the audience?

DR. LaRUSSA: This is Phil LaRussa. I would like to make a formal request to have a workshop on a quadravalent vaccine. How do we go about getting that?

ACTING CHAIR KARRON: Well, I guess the question would be -- and I will pose this question to Dr. Midthun. Would it be appropriate for us to make a motion that the FDA consider convening a workshop with interested stakeholders to further discuss this issue? Is that appropriate?

DR. MIDTHUN: You can make a recommendation. Sure. Absolutely.

ACTING CHAIR KARRON: Okay. Would that be something that we could vote on or is that useful?

DR. BAYLOR: This is Norman Baylor. I think, to just make the recommendation -- I don't think we need total numbers, but as a recommending body, you could make the recommendation that FDA follow through with planning a workshop to discuss the quadravalent. That will be in the transcript. So that's on the record.

ACTING CHAIR KARRON: Okay. Yes, Dr.

Coelingh.

DR. COELINGH: Question for clarification. The materials that are provided us at the meeting are tremendously useful, and the discussions that happen here, to the manufacturers. We actually go back to these documents over and over again to look at how strains behave antigenically.

So my question is: Will the materials that were shown today be updated on the website?

DR. WEIR; Yes. I was going to make that point, that we put together all of this pretty fast this week, since we had the WHO meeting earlier, and we will get it updated and back out to both the Committee members and onto the website.

ACTING CHAIR KARRON: So, actually, to go back to Dr. LaRussa's point, my sense just from listening to Committee members is that there is a consensus that we would like to ask the FDA to consider convening a workshop to discuss the possibility of a quadravalent vaccine. Am I correct in assuming that? I will assume that I am unless I hear anything from any other Committee members at this

time.

DR. COUCH: Well, your comment on the quadravalent -- Couch again. It may be minor, but it bothers me a little bit to say that the workshop will address quadravalent vaccine, rather than address the question of how to optimally vaccinate against the two lineages which appear to be jockeying for control in any given year.

It may be alternate years, you know, prime the first year and give them the other one a second year, but a little more open-ended discussion rather than just the question of quadravalent.

ACTING CHAIR KARRON: Thank you very much. I think that is a point very well taken.

DR. COUCH: Could I add one other comment while I'm at it, again one that used to be heard annually from Ed Kilbourne, who doesn't sit in anymore. But CDC gives us the data now pretty regularly that the neuraminidase is not showing any major changes that would give us concern for which strain we pick for primarily targeted toward the hemagglutinin, and the hemagglutinin antibody in all

of our minds is the dominant and desired antibody to have in this population, but the neuraminidase antigen is in the vaccine, and we hope it is active in each of the preparations that is marketed and distributed, but we are not monitoring the neuraminidase antibody responses, and we are not doing anything to be sure that that antigen is present and active in adequate quantities.

While it is not the essential antibody, it is a highly desirable antibody and, as Ed says, we ought to keep that one in mind as varying less than the hemagglutinin does, and perhaps the back-up against a hemagglutinin variation that caught us by surprise, whereas the neuraminidase did not vary.

ACTING CHAIR KARRON: Thank you. Other comments?

MR. THOMAS: This is Albert Thomas from sanofi pasteur. I just have one question on the presentation from Dr. Ye regarding the status of candidate vaccine strains. Specifically, for the H3N2, the A/Wisconsin/67 and the A/Hiroshima/52, there is no information available for the potential growth

of that -- of those two strains. I was wondering, is there any new information that could help fill that in?

DR. YE: Actually, TGA is conducting the reassortant of Hiroshima, but at that point I don't know what is the updated status. You refer to Wisconsin. I don't know.

DR. KLIMOV: This is Dr. Klimov. Dr. Dorothy Bucher in the Medical School in Buffalo -- she is preparing the Wisconsin/67 reassortant right away, right now. I don't have yet final data. As far as I know, she is at the stage of final cloning or purification of those reassortants. We hope to receive them sometime very soon for antigenic analysis, and detailed genetic analysis.

DR. YE: This is Ye. Yes, Sasha, you are right. Dorothy Bucher in New York Medical Center is conducting the reassortant for the Wisconsin virus.

ACTING CHAIR KARRON: Any other comments?

MR. MOORE: This is Rich Moore from sanofi pasteur, and I would just like to remind everyone that we are talking about a 120 million dose capacity

nationwide. However, that was based on the best yielding A strain we've ever seen before, the A/New York, as well as the best yielding B strain we've ever seen before, the B/Jiangsu, and there's been years in which the strain doesn't yield as well.

I think some of these people who have been there for a while will remember those years, and I think there is a little concern on our part that we don't know the yield of the reassortants that are being made, the Wisconsin-like or Hiroshima-like viruses; and it is possible that they could be very low.

In that case, I wonder if we would at least consider having the New York a Wisconsin-like virus? In the WHO website, it was only a twofold difference. That's enough to qualify it for "like." I know it does depend on when you run the test and all that, and it is maybe a threefold difference, but only as a fallback position, if the yield is really poor for the reassortant, that we might consider that as a fallback position so that we don't have, you know, 20 million doses total for the U.S.

DR. WEIR: This is Jerry Weir. I'm not sure that we can have a fallback position if we've recommended a change to a different strain like that, as that recommendation was based on the serological data and the surveillance data. I don't know if anyone else has something to add to that or not.

DR. COX: This is Nancy Cox. It would not be -- It would be a fallback position which would require an additional convening of the panel, because the way that the WHO and I think the way that we are looking at the data is that this is an advance. Viruses have moved on, that we recommending an update based on all of the epidemiologic, antigenic, serologic and virologic information. So that fallback position would not be consistent with the WHO recommendations and would require that we discuss it.

ACTING CHAIR KARRON: It would also not be consistent with our VRBPAC recommendations.

DR. COUCH: This is Couch. I would hope that we would have enough flexibility that, if we really get caught on something, we can reconsider the subject.

DR. COX: But it would require reconvening the panel.

DR. COUCH: Convening by phone was actually relatively quick and relatively easy.

ACTING CHAIR KARRON: Sure.

DR. COX: Two years ago, I think --

DR. COUCH: It was two years ago for me. We had a conference call later on to finalize the recommendations. So we could do that.

ACTING CHAIR KARRON: I think the point is only that it would be really a strain change, and we would -- it would require us to reconvene to discuss it. I think that is the point.

DR. COUCH: My point that I would hope we would make is that we don't want to rigidly lock this subject into a poor vaccine supply. We need to have enough flexibility to consider the alternatives that need to be considered after today.

ACTING CHAIR KARRON: Yes. Okay.

DR. COX: Just one more thing. I know, historically, we have had conference calls as late as, I think, March 10 to finalize the strains, and perhaps

even a bit later. So we have in the past when we have found it necessary to convene an additional conference call gone at least that far into the season in order to finalize vaccine strains.

ACTING CHAIR KARRON: Thank you. Actually, at this point, unless there's any further discussion on this topic, I would like to ask you, Nancy, to give us an update on H5N1.

DR. COX: Okay. Thank you very much. We will have to go back to the CDC slide presentation on page 32. I will give you just a moment to get that up on your computer, and we will go straight to H5N1.

If you will look at Slide 33, you will see the cases, the human cases, that had been confirmed up to February 3, 2006, represented by red dots in the countries Cambodia, China, Thailand, Vietnam, Indonesia, Turkey, and Iraq, which are the countries that, at least as of that date, had reported human cases.

This is a rather dramatic increase in the number of cases and the numbers of countries which reported human cases since last year. I would like,

because I have not been able to -- I'm taking this call remotely and have been in transit for a good bit of the last 36 hours, and so I would like to ask Dr. Klimov from the CDC, who has just pulled up from the WHO website the official numbers of cases by country, to report on those numbers for you. Sasha?

DR. KLIMOV: Yes. Hi, Nancy. So the most updated table at the WHO website is from February 13, the same date you are showing the map. So the numbers are: Total numbers of laboratory confirmed H5N1 cases total is 169. Of those, 91 are fatal cases.

I will go through all those countries very shortly, and the first number will be number of cases. The second number will be fatal cases.

Cambodia: They had in 2005 four cases, four deaths. China: Total, 12; eight deaths; Indonesia: 25 cases, 18 deaths; Iraq: one case, one fatal case; Thailand: 22 total, 14 fatal; Turkey: 12 total, four fatal; Vietnam: 93 total, 42 fatal.

Thank you.

DR. COX: Okay, thank you, Sasha.

As you can see, the mortality rate -- the

case fatality rate continues to hover around between 50 percent and 70 percent. As cases flood in from different countries, the proportions change by total and by country, but certainly, the case fatality rate has not dropped terribly dramatically. It has remained very high overall.

We know that case ascertainment is probably relatively poor in many of these countries, and that there could be asymptomatic or mild cases as well as severe cases that are being missed in areas with relatively poor surveillance.

If we go to the next slide on page 34, what you will see here is data up to the same time showing in green the countries that have reported poultry or wild bird cases, and I believe there are a couple of additions not shown here, and that would be Austria and Germany which reported cases in wild birds yesterday, I believe, or the day before.

Then the countries shown in yellow -- sorry, red are those countries which have both human and poultry cases. Japan and South Korea have both effectively stamped out H5N1 high path outbreaks in

poultry.

So it shows that it is possible to do so with aggressive stamping out measures and excellent surveillance. But you can see that, compared with last year, we have vast regions of the globe which are now affected or into which H5N1 has been introduced, and the belief is that the introduction of H5N1 viruses into the Middle East and Europe has occurred through the migration of wild birds which are carrying the virus along the migratory routes that are fairly well described in the literature.

So I would also like to point out that there is a great deal of concern, since H5N1 has now been detected in Africa, in West Africa, and there are a number of rumors of bird die-offs in East Africa along the migratory routes, as well as additional rumors of H5N1 in countries in the Middle East where H5N1 has not been confirmed.

Although I lost my Blackberry connections en route to my destination, I did note that there are also rumors of large bird die-offs in India at the moment.

So I am sure it will be a changing picture day by day, and while many in Europe had considered that it was safe to have poultry outside because the migratory season had already ceased, because they have been finding dead wild swans that have been demonstrated to be infected by H5N1, many of the countries in Europe have ordered the farmers to bring the poultry -- make sure the poultry remains inside so that they are less likely to become infected by wild birds.

If you move on to the next slide -- and there is one more thing about that slide that I wanted to mention. HHS and CDC have received additional dollars from the Congress to enhance surveillance in countries which have already experienced H5N1 outbreaks or in neighboring countries where H5N1 outbreaks may be expected to occur.

All of those countries which have the hatched lines in them have bilateral agreements with the U.S. which are actually in the form of cooperative agreements where money is provided to the countries to expand their surveillance networks into more rural

areas and to capture not only seasonal influenza isolates but also H5N1 cases, should they occur.

As a result of this initiative, we are receiving many more viruses from some of these countries than we have in previous years, and certainly have received H5N1 viruses from many of the countries that have had human cases. Next slide, please.

When we look at the evolutionary relationships of the HA genes in these circulating viruses, we are seeing a great deal of genetic diversity, and that will be reflected in the antigenic table which I show next.

If you concentrate at the very bottom of this dendrogram, what you will see listed at the very bottom is China avian virus which looks like the ancestor of all of the current strains. That virus is actually the Goose Guangdong '96 virus which caused outbreaks in geese, in domestic geese, in south China in 1996, and that really is the granddaddy of all of the viruses that are circulating throughout Asia, the Middle East and Europe at the moment.

Then you will see right above that the Hong Kong '97 viruses and, of course, we are all very familiar with the outbreak that occurred in humans in Hong Kong in 1997 and resulted in large scale culling of all the poultry in Hong Kong on a couple of occasions.

Then you will see the rest of it, the majority of the dendrogram is comprised of viruses primarily isolated in 2004 and 2005. The viruses at the top that are bracketed and labeled as clade 1 viruses are those that caused the human outbreaks in 2003 and 2004, and you will see there near the top of clade 1 a virus in red and in bold which says "Vietnam 120304," which is one of the vaccine reference viruses that has been used to make pilot lots and has been used in clinical trials in the United States and a related virus, Vietnam 11/94 has also been used.

Now, of course, it wasn't a wild type virus itself, but it was a reverse genetics modified virus in which the multi-basic amino acid cleavage site in the hemagglutinin was removed, and then that hemagglutinin and the neuraminidase from the H5 were

rescued on a PR8 backbone, and the viruses were very carefully tested for safety and then provided to manufacturers to make pilot lots of vaccine which were used in clinical trials.

I'm sure you have heard some information about those human trials in the news, although the results have not yet been published in the scientific literature.

Now if you will direct your attention to the bottom of the dendrogram where it says "Clade 2," you will see a group of quite genetically diverse viruses comprised of viruses from Vietnam, from China, from human cases in China, from both avian and human cases in Turkey, and you will see a number of avian viruses from Rumania, Mongolia, Russia, and so on.

Toward the top of Clade 2, you will see a number of viruses, both from humans and from birds, from Indonesia, and you will see one virus which is in red and bold, and that is the Indonesia/505, and that is the particular strain that was used by our laboratory at CDC to make a reverse genetics modified vaccine candidate.

So in short, if I could summarize the genetic properties of the hemagglutinins and the neuraminidases, the genetic properties of the neuraminidases track very closely with the genetic properties of the humagglutinins. You can see that they fall into two major genetic groups, Clade 1 and Clade 2, and then Clade 2 is more diverse than Clade 1, and there are a number of subgenetic groups in Clade 2.

Now moving on to the antigenic analysis shown in Slide 36, we have color coded the Clade 1 and Clade 2 viruses. So at the top left of the HI table, you will see Vietnam/1203, Vietnam/Japan/30321, and Vietnam/30408. Those are all Clade 1 viruses, and those were Clade 1 viruses that showed the greatest antigenic diversity among Clade 1 viruses that we tested.

The Clade 2 viruses are represented by antigens 4, 5, 6, 7 and 8, most of which are from Indonesia. Among those antigens you will see Indonesia/5 which I had pointed out before, which is the second Clade 2 antigen shown in the green box, and

then Indonesia 5-R, which is the far right, in the far right column, and that -- So that antiserum was made to our reverse genetics modified Indonesia/5 vaccine reference virus.

So you can see very clearly from this HI table that there are -- that both antigenically and genetically we can distinguish Clade 1 viruses from Clade 2 viruses, and that cross-reactivity between Clade 1 viruses and Clade 2 viruses is relatively poor.

I can substantiate that statement by saying that we have taken serum from an individual who had recovered from an infection by a Clade 1 virus and have used that serum in a serum in a microneutralization assay, and whereas we had high titers of microneutralizing antibody against Clade 1 virus, homologous virus, we found that the neutralizing antibody titers to viruses in Clade 2 were reduced significantly.

So that was really the basis for the development of not only Clade 1 viruses as vaccine candidates, but also more recently Clade 2 viruses as

potential vaccine candidates that could be used to make pilot lots and then subsequently be used in human clinical trials.

We went over some information at our WHO meeting which I will summarize briefly. Rob Webster has been working on two potential vaccine candidates in Clade 2, one from Mongolia and one from China. They have rescued -- removed the multi-basic amino acid cleavage site and rescued a virus for both of these wild type strains, and their viruses are awaiting test -- both viruses are awaiting testing.

At CDC our Indonesia/5 virus has gone through the full battery of safety testing, which includes demonstrating that the virus -- the reassortant does not plaque in the absence of trypsin, that it does not kill chick embryos, that it is apathogenic when inoculated in chickens, and is not pathogenic in ferrets; and we have prepared a dossier and have submitted it to USDA to gain select agent exemption, because, of course, in the United States highly pathogenic avian influenza viruses are considered to be select agents, and so in order to be

able to ship the virus to manufacturers, we must obtain official paperwork from USDA exempting the vaccine candidate from the category of select agent.

We may already have that paperwork back from USDA. I'm not sure. perhaps Sasha could update us when I finish the summary.

In Japan, they chose the Indonesia/6, which is shown in the HA table right sort of in the middle of the Clade 2 viruses in the HI table, and they went ahead and rescued a virus, but there are some concerns that have arisen in Japan about genetically modified organisms. So they have hit a regulatory snag.

In the UK, they have also hit a bit of a regulatory snag, and there the virus that they have rescued had to be rescued in a back-up facility. So there is a question about whether or not the regulatory authorities will accept it or not, because it was prepared in a laboratory but in a glovebox and under very stringent conditions, but there was another glovebox in the same room where another virus was being worked on at the same time.

So it just depends on the determination of the regulatory authorities as to whether that will be acceptable or not, and that virus has not been tested in -- that virus has not been tested in ferrets yet, and they use the Turkey/2005 virus.

So the bottom line is that there is one Clade 2 virus that is almost ready to be distributed to manufacturers. There are others that need to be tested in ferrets but should be -- the testing should be complete shortly, and then select agent exemption would have to be obtained for the U.S. ones, and then the one in Japan and the one in the UK which have some regulatory concerns surrounding them.

So I think that is a complete update. With that, I will close, and entertain any questions.

DR. KLIMOV: Before any questions, I should say that as of yesterday the FDA excluded the reassortant in Indonesia/5/2005 PR8 genetically modified reassortant from the select agent list.

DR. COX: So that means that we can distribute that virus to manufacturers and others under a standard material transfer agreement.

ACTING CHAIR KARRON: Thank you very much. Are there questions for Dr. Cox? I actually have one question.

I was just wondering, Nancy, whether at the WHO meeting -- have you heard any reports about different clinical presentations or outcomes between Clade 1 and Clade 2? Was there any discussion of that?

DR. COX: There has been discussion, not specifically at that meeting, but it appears that, at least superficially, from what we've been hearing about case presentations and outcomes and the spectrum of illness, it seems that there are great similarities both from disease caused by Clade 1 and Clade 2 viruses, but also in the disease that was caused in 1997.

There are some atypical cases reported in the literature where respiratory symptoms were not reported, but in one case encephalitis and in another case where diarrhea was a very prominent feature. But I think that is perhaps simply because we are accumulating many more cases than we had in the past,

and so we are seeing certain cases that present in what may be a slightly atypical manner.

ACTING CHAIR KARRON: Thank you. Other questions or comments? There is a question from the floor.

MS. HO: Hi, Nancy. This is Meishang Ho from Taipei. My question is: At the bottom there are two isolates from China, and the titers are low. So what do we know about it for human isolates from China? Do they fall -- I guess you can find -- There are lots of China isolates on the top, but there are only two that have been tested.

DR. COX: There are two which we have at CDC which have been provided to us. We are expecting additional human isolates to be provided to us from mainland China. Those viruses are actually in a little bit different part of the evolutionary tree than the Indonesian viruses and the Turkey viruses.

I actually was -- Even though the titers against the Indonesia/5 are a little bit reduced for a couple of the viruses, one of the Turkey viruses and the Anhui/2 virus, I was relatively pleased that the

Indonesia/5 antiserum tends to cover the majority of the human isolates fairly well.

So I was afraid we were going to see even more diversity than we have among the human isolates. So our test antigens that we have included in this particular test are all isolates from humans.

Now if we take the full gamut of viruses and include more viruses that have been isolated from birds, you don't see quite as -- you see greater diversity, I would have to say.

We have had much -- I would like to say that we have had a great deal of transparency in our interactions with Indonesia and with Turkey, and certainly much greater transparency in our interactions with China than in some previous situations, and it has been very positive.

I am not sure that answers your question, but those -- the bottom line is those viruses are genetically a little different, and they are antigenically a little different, but I think they are pretty well covered by the Indonesia antiserum. So at least I think we have a good shot with that particular

vaccine candidate, if it is immunogenic, to induce antibodies that would be fairly broadly cross-reactive against different groups of viruses.

MS. HO: Well, Nancy, if this were placed in the group of H3, we would have seen fourfold drop. We will see that we will call that a low reactor, and now -- because China has -- You know, there are only two viruses down here. Maybe more needs to be looked at.

DR. COX: Oh, absolutely, and we have now -- They have set a precedent by sending the viruses, and have promised follow-up with additional viruses. So we are trying very hard to get viruses both from the human health authorities and the animal health authorities in China. And although there is a fourfold drop with Anhui/2 -- and you are right -- we would consider that to be significant.

What I was really afraid of, honestly, in looking at this great deal of genetic diversity, that we wouldn't find an antiserum that would cover even this well. So if you see what I mean, my expectations were fairly low, given the genetic diversity that we

are seeing.

My feeling is that a lot more needs to be done. We need to continue to gather viruses from as many human cases as possible, to continue to do the cross-testing with post-infection ferret serum, and determine if it is really necessary to make multiple -- not just one Clade 1 vaccine reference strain, but multiple vaccine -- multiple Clade -- sorry, not just one Clade 2 vaccine reference strain, but multiple Clade 2 reference strains for cross-reactivity in animal models and potentially in humans.

ACTING CHAIR KARRON: Thank you. Are there any more questions for Dr. Cox?

There is one comment by Dr. Baylor.

DR. BAYLOR: And this is just sort of a statement and a brief update of reactivity to address pandemic at the FDA.

We are moving forward with developing guidance documents, and those have moved quite far in guidance documents to address the regulatory requirement for licensing pandemic influenza vaccines, as well as a guidance document on licensing the

standard trivalent inactivated vaccine.

So that activity is moving forward. Also, the FDA did receive a supplemental budget -- not an increase in the budget, but a supplement from the Department to increase our activities to facilitate the development and evaluation of new vaccines for influenza pandemic.

So we are working with our international partners as well as our partners like CDC and others in the Department to move those things forward.

ACTING CHAIR KARRON: Thank you. If there are no other comments, I think we will adjourn the meeting. Thank you all for attending, and we are adjourned.

(Whereupon, the foregoing matter went off the record at 4:22 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/CBER

Date: February 17, 2006

Place: Bethesda, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.